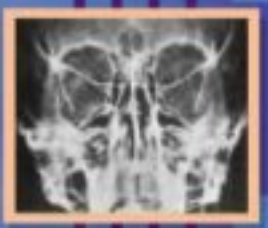
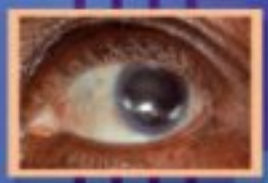
SECOND EDITION

CLINICAL MEDICINE IN OPTOMETRIC PRACTICE





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CLINICAL MEDICINE IN OPTOMETRIC PRACTICE ISBN: 978-0-323-02961-2

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The Publisher

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Library of Congress Control Number: 2007922500

Publishing Director: Linda Duncan
Senior Editor: Kathy Falk
Senior Developmental Editor: Christie M. Hart
Publishing Services Manager: Pat Joiner-Myers
Senior Project Manager: David Stein
Design Direction: Teresa McBryan

Printed in China.

Last digit is the print number: 9 8 7 6 5 4 3 2 1

To my son,

Jordan Alexander,

Who always tickles sleeping dragons

Preface

BACKGROUND

The first edition of *Clinical Medicine in Optometric Practice* was conceived amidst a storm of controversy. Two decades ago the political climate surrounding the field of eye care was fiercely antagonistic, as forces fought to suppress the right of optometrists to prescribe appropriate topical and systemic medication. With battle lines drawn in every state legislature across the nation, optometrists slowly and deliberately gained the diagnostic and therapeutic privileges that would benefit their patient population.

The increased responsibility inherent in the prescribing of topical and systemic medications mandated a familiarity with systemic disease conditions. To achieve this goal, the first edition was proposed and structured to fill the educational needs of both the optometry student immersed in a clinical medicine curriculum and the doctor in the field who sought comprehensive descriptions of systemic disease.

In 1988 Mosby identified the need for such a book. I was fortunate enough to be asked to edit and contribute to the first edition of what would become a landmark in optometric literature.

From the outset, the first edition reflected the political strife besetting the entire profession. The medical community was up in arms about this text, claiming that optometrists had no right to the information presented within its pages. During the 5 years it took to bring the book to life, several medical authors dropped out of the project due to political pressure. One editor of the first edition had a surgeon from a prominent Philadelphia-based eye hospital enter his office and threaten never to publish with Mosby again if they dared to publish *Clinical Medicine in Optometric Practice.* Fortunately my editor refused to cave into the pressure and the book did get published.

WHO WILL BENEFIT FROM THIS BOOK?

In the past decade, *Clinical Medicine in Optometric Practice* has emerged to become the best selling text on systemic conditions and the eye written exclusively for the optometrist. Copies have found their way into the hands of students and optometrists the world over. I have been gratified to learn that the first edition has influenced the education of thousands of students and has been a valuable resource to those already in the field.

And now the second edition, conceived in a medical environment far different from the first, is poised to contribute to a second generation of students and doctors. To those familiar with the first edition, they will find a completely new and reformatted text. The book has been completely rewritten with new and indispensable information on systemic conditions that influence the eye.

To those who are seeing the book for the first time, the second edition will serve to familiarize the student and the optometrist with the ocular signs that indicate possible underlying systemic conditions. Beautiful color photographs highlight the descriptive text.

ORGANIZATION

The reader will note that the book is now divided into four parts. Part 1 discusses the medical diagnostic armamentarium available to the optometrist, from physical diagnosis to laboratory testing and radiology. Part 1 emphasizes the integration of these strategies into the optometric work-up.

Part 2 concentrates on the medical specialties that impact on eye care. Here are presented the pathogenesis and evolution of systemic disorders, which serve to sensitize the optometrist to the myriad of symptomologies indicative of underlying disease. I wanted this section of the book to help an optometrist faced with patients who are, by virtue of their history and symptomology, suspicious for systemic disease. In addition, by examining the most recent diagnostic and therapeutic regimens available, Part 2 serves as a quick reference guide for eye care practitioners and helps them gain familiarity with the medical conditions of their patients.

Part 3 addresses the most likely scenario for the eye care practitioner: the patient who presents with an ocular disorder that itself is suspicious for systemic disease. This section examines the possibility that the

patient's anterior or posterior segment pathology is related to a systemic condition. By identifying the eye pathology, these chapters will guide the optometrist back to the appropriate chapters in Part 2 that describe the possible associated systemic disorders.

New to the second edition, Part 4 examines the latest information on the hottest topics in optometry. These include eye care for the pregnant patient, genetics in optometry, injections, and drug side-effects.

Since the fundamental philosophy guiding *Clinical Medicine in Optometric Practice* is an attempt to unify primary optometry with clinical medicine, I sincerely hope that this book symbolically foreshadows an age of enlightened eye care delivery. May all our patients benefit from the knowledge contained herein.

Bruce G. Muchnick, O.D.

Acknowledgments

The completion of this text is due in no small part to a great number of people who helped in its production. First and foremost, I wish to acknowledge and gratefully thank the authors of the first edition of this book. Without their expertise and invaluable contribution, *Clinical Medicine in Optometric Practice* would never have become the most influential textbook in optometry history. In particular, a special thanks to some of the finest authors I ever had the pleasure to work with: Drs. Connie Chronister, David Bright, Jerry Cavallerano, Brian Mahoney, John McGreal, Leonard Messner, John Nishimoto, David Sendrowski, and Ronald Serfoss.

I wish to thank the hard-working editors at Elsevier; Ms. Christie Hart and Mr. David Stein.

Many thanks to Mr. Sam Mohr, Ms. Dione Bailey, Ms. Henrietta McBall, and Ms. Christie Milligan of the Coatesville Veterans Administration Medical Center for their assistance in producing many of the clinical procedures photographs in the text.

I must offer a special acknowledgment to Dr. Christopher Rinehart and Dr. Pierrette Dayhaw-Barker for suggesting me as author of this text.

We stand in the shadows of optometric educators who came before us and continue to inspire us to this day. These people, our mentors, should never be forgotten. I have been most fortunate in my career to work with some of the best in our profession: Dr. Lorraine Lombardi (who despite the advent of computer technology can still draw the human brain "DaVinci-like" with two hands at the same time), Drs. Gilda and the late George Crozier, the late Dr. John Crozier (who always believed in me), Dr. Louis Catania (who gave me my first lecture assignment), Dr. Linda Casser (the most brilliant optometrist I ever had the honor of working with), Dr. Andrew Gurwood (the most dedicated optometric educator I have ever had the privilege of knowing), and the late, great Dr. Lawrence Gray. Also, special thanks go to the late Dr. Samuel Cutler, Dr. Nibondh Vacharat, Dr. Richard Sowby, and my personal mentors: Drs. Christopher Rinehart, Jeffrey Nyman, and Bernard Blaustein, who all taught me much about the history and practical aspects of optometry and medicine.

CHAPTER 1

The Optomedical History

CHAPTER OUTLINE

The history helps to form the clinical basis for the differential diagnosis of the patient. Every piece of information made available to the examiner must be used to create a clinical approach tailored to the patient's own unique profile. The history may yield the presence of symptoms that indicate a disease state. If the patient is seen with a known disorder, the history may help to determine the extent and prognosis of the disease. In cases in which therapy has been instituted, the history is used to help determine the effectiveness of past or present treatments.

Nonetheless, the history can be hampered by significant patient limitations, such as poor historical recall and inadequate explanations. In addition, poor fact gathering and inappropriate interpretation by the examiner further complicate the gathering of information.

The ability of the patient to completely recall his or her past medical history in detail is desired but rarely achieved. The passage of time will tend to cloud even significant memories, so that a patient will have difficulty in recalling surgeries and medical treatment. For example, it is not unusual for patients who have undergone a cataract extraction to quickly forget that the procedure was ever performed. In general, elderly patients will have difficulty with historical recall. The examiner can help stimulate memories by asking which doctor the patient had seen and in which hospital the procedure was performed. To obtain information about past

medical situations, it often helps to ask the patient to attempt to visualize the memory.

The patient may inadequately describe his or her past medical history. The examiner should repeat back to the patient any information that is not logical, as this might stimulate the patient to better recall. The examiner may wish to verify certain facts with relatives, although this should be done with respect and sensitivity to the patient.

The examiner may expedite information gathering by taking a well-organized history in a non-stressful environment. Effective doctor-patient communication improves the gathering of medical information. Appropriate body posture, proper eye contact, the clear display of sympathy, and the ability to keep the patient focused on the subject are essential.

The examiner should strive to minimize interpretation of the patient's responses when taking the medical history. A wrong interpretation may lead to faulty logic. Instead, the examiner should record the patient's exact words in quotation marks, followed by the examiner's logical deduction in parentheses, to minimize interpretive errors. For example, an accurate recording in quotation marks of the patient who says, "I see cobwebs moving around in my vision," can be followed by the examiner's interpretation of that symptom (possible floaters). Some might argue that no interpretation of the patient's information should occur during the history, but in a practical setting this is virtually impossible. The patient often uses inflections and hand movements that cannot be adequately recorded but that might support an interpretation. The examiner should minimize interpretation to avoid false assumptions.

A reiteration and summary of the patient's history before the examination will help to stimulate the patient's historical memories and confirm certain facts.

Ocular manifestations of systemic disease are common; therefore the optometry examination mandates a two-part history comprised of both eye and medical information. Such a history can be complex; thus the examiner needs an organized approach. This chapter outlines the elements of the optomedical history and the integration of these elements into the optometry examination.

PATIENT PROFILE

Age

The accurate recording of the patient's age is significant because of the chronological distribution of disease states. Pathology is often age-dependent, and an understanding of which disorders are most common in each age group can help the examiner in his or her differential diagnosis. For instance, hereditary and congenital disorders are often first diagnosed in childhood. Adolescents, who are particularly prone to risk-taking behaviors, have a higher than average rate of motor vehicle injuries to the face and neck and are significantly susceptible to depression, migraine headaches, certain cancers, respiratory ailments, tobacco and alcohol use, sexually transmitted diseases, unhealthy dietary habits, and exercise-induced heart disorders. The middle-aged patient is prone to develop high blood pressure, thyroid conditions, cardiovascular disease, and Type II diabetes mellitus. Elderly patients are likely to manifest symptoms and signs of brain atrophy, certain forms of cancer, and cerebrovascular and carotid disease. Despite the tendency of some disorders to cluster in certain age groups, the examiner should use the age of the patient only as a clue in developing a differential diagnosis.

Race

Some disorders are more common in certain racial groups; thus an accurate racial determination may help in the differential diagnosis. For example, glaucoma occurs earlier and in greater frequency in the African-American population than in whites, but the prevalence of age-related macular degeneration is highest in the white population. Despite the obvious medical necessity to record race, patients may be sensitive when the subject is raised. Education may be a valuable tool to ease patient anxiety. For instance, the examiner might explain that a patient of mixed heritage may be prone to diseases that affect both races.

Sex

Most research studies on diseases and pathophysiology have traditionally included only male subjects. In recent years, medical issues involving women's health have gained increasing attention. Significant differences between men's and women's health issues have become obvious. For example, during the past 60 years, cigarette smoking, which is a major risk factor in cardiovascular disease, has sharply declined in men, but not in women. This fact may explain why ischemic heart disease remains the leading cause of death in U.S. women older than 65 years.

Occupation

Environmental and occupational hazards strongly influence eye disease. The patient's occupation may yield clues to the causes of ocular, neurologic, and systemic manifestations. The examiner should ask the patient what type of work he or she is engaged in, ask about the timing of any symptoms related to work, and ask about exposure to environmental agents such as pesticides and chemical agents. The usefulness of a

thorough occupational history is exemplified by the case of a 19-year-old college sophomore who was seen in our clinic complaining of blurry vision and a loss of dexterity that resulted in chronic misplacement of objects. All optometry and neurology testing was normal, except for reduced visual acuities to 20/25 in both eyes. An examination of the patient's workplace at her college chemistry lab found a fine crack in the hood designed to protect her from exposure. Replacement of the hood resulted in eventual return of normal vision and return of her normal dexterity.

REASON FOR VISIT

Chief Complaint

The chief complaint is the reason for the patient's eye examination. Although the prime motivator for the patient's visit, the complaint may not represent or even be associated with the ultimate diagnosis. The chief complaint may seem significant to the patient, and is obviously troublesome enough to warrant an examination, but may eventually be relegated to a minor diagnosis compared with what is eventually uncovered (Box 1-1).

The examiner should never forget to address all the complaints of the patient, even if a sight- or life-threatening condition is found that is unrelated to the chief complaint. For example, a 42-year-old African-American male who was seen in our clinic complained that he had dry eyes on awakening. The confrontational visual field examination showed that the patient had a superior, bitemporal quadrantanopsia. Radiological testing revealed a pituitary tumor. Weeks later the patient returned after successful surgery, and the visual fields were normalized. The patient remarked that he still had dry eyes, however, and that his chief complaint was never addressed. Artificial tears were prescribed and were successful in ameliorating his symptoms.

BOX 1-1
IMPORTANT HISTORICAL QUESTIONS

Describe the symptom or episode.
When did the symptom first begin?
How did it first occur (how did it come on)?
How does the symptom subside (gradually vs. suddenly)?
When did it last subside?
How many episodes of the symptom have occurred since the first episode?
Are the symptoms or are the episodes getting worse, better, or staying the same?
Are episodes increasing or decreasing in frequency?
What, if anything, triggers the symptom?
What, if anything, relieves the symptom?
Are there any concurrent, associated symptoms?
Where is the symptom located?
Has the symptom changed over time?
Have you seen a health-care professional for the symptom?
Have you undergone any therapy for the symptom?
Does the symptom occur during any particular time of the day or night?
Can you do anything that changes or modifies the symptom?

Location

Every attempt should be made to isolate the location of the symptom. The examiner should record the location in unambiguous anatomical terminology. It may be difficult to pin down a precise location, because the patient may indicate a near-global area of involvement. For example, the patient with a headache may be unable to point to a precise location of the pain, and instead note that the entire head is involved.

Quality

The examiner should record the way the patient describes the characteristics of the symptoms. The description usually consists of an adjective, so that, for example, the symptom of pain is described as "sharp" or "dull."

Severity

The severity of the symptom can be difficult to assess, because the patient may have trouble quantifying this characteristic. The examiner may wish to ask the patient to rank the severity of the symptom on a scale of 1-10, with 10 being the most severe pain the patient can imagine. The examiner should note the response as "the patient reports the pain is a 7 out of 10." Standardized scales exist that have been accepted in the literature for various symptoms, but the inherent problem with these scales is that they assume all examiners are aware of and use these systems.

Duration

The length of time from onset to cessation of any symptom should be recorded. The duration of a single episode of the symptom should be differentiated from the frequency of the episodes since first onset. For example, a patient's headache may have a typical duration of 2 hours, but the headaches may have occurred for many years.

Timing

The patient should be asked whether the onset of the symptom occurs at any particular time of day. In particular, the symptom may occur most commonly on awakening, and be best described as a "morning

symptom." Other symptoms may not be noticed until later in the day or in the evening. This timing is crucial in determining a possible causative factor that is related to the patient's life-style or to circadian rhythms.

Context

The patient should best judge the environment in which the symptom most frequently occurs. For example, a patient with dry eyes may notice the onset of symptoms only in the work environment, or a patient with headache may observe that the pain occurs only at high altitudes.

The context in which the symptom occurs can be used to help determine an underlying etiology.

Modifying Factors

The patient should try to determine what factors contribute to the onset of the symptom, modify the symptom during the episode, and help to relieve the symptom. These modifying factors may be environmental, pharmaceutical, psychological, or logistical in nature.

Associated Symptoms

Symptoms rarely occur in isolation, and the patient should be encouraged to detail any other problems that occur at the same time or within the same symptomatic episode. The examiner should attempt to determine whether these mutual symptoms are coincidental or temporally related. Associated symptoms help in the creation of a differential diagnostic list and in the determination of an underlying etiology common to at least some of the symptoms.

OCULAR HISTORY

The examiner should review the personal ocular history of the patient. This history includes ocular surgery, past ocular diagnosis, history of strabismus, past ocular injuries or trauma, the present spectacle and contact lens prescription and type, and the history of past ocular therapy with medications or laser. The date of the last eye examination and the name of the examining doctor will help the examiner to determine the patient's level of compliance and to retrieve past medical records.

REVIEW OF SYSTEMS

An efficient review of the patient's systems is necessary to explore the possible relationship between ocular symptoms and systemic disease. The reviewer should encourage the patient to recall any relevant symptoms, diagnoses, or treatment pertaining to each system that is reviewed.

Constitutional

This somewhat archaic term pertains to the overall health of the patient and is used to describe the general well-being of the patient.

Eye

Common abnormal ocular symptoms include blurry vision, double vision, eye pain or itch, flashes and floaters, photophobia, color vision problems, sudden or gradual vision loss, or difficulty with nighttime vision. Past diagnoses may commonly include uveitis, cataract, glaucoma, corneal infections, or retinal detachment.

Ears, Nose, Mouth, and Throat

Relevant symptoms include ear pain, mouth sores, hearing loss, loss of taste, loss of smell, throat pain and throat lumps, nasal discharge or pain, and excess production of ear wax. Known diagnoses typically include infections, tumors, environmental causes, neurologic loss of senses, pharmacologically induced loss, and inflammations from systemic diseases.

Cardiovascular

Symptoms include chest pain, palpitations, difficulty breathing, easy fatigability, and arm or back pain (particularly, but not necessarily, related to exertion). Past diagnoses include angina, myocardial infarction, systemic hypertension, coronary heart disease, and valvular heart disease.

Respiratory

Symptoms include shortness of breath, coughing, coughing up of blood, and chest pain. The most common diagnoses include asthma, cystic fibrosis, sarcoidosis, myasthenia gravis, and chronic obstructive lung disease.

Gastrointestinal

Gastrointestinal (GI) symptoms include obstruction to solids or liquids on swallowing, nausea, vomiting (because of pregnancy or pseudotumor cerebri), indigestion, diarrhea, constipation, gastric pain, weight loss, jaundice, and abdominal swelling. Common GI diagnoses include tumors, ulcers, injury, Crohn's disease, GI infections, drug and food allergies, inflammatory bowel diseases, and mechanical difficulties in swallowing.

Genitourinary

Symptoms of genitourinary problems include fever, genitourinary pain, bladder pain, pregnancy, blood in the urine, abnormal discharge, difficulty in voiding, incontinence, erectile dysfunction, disturbances in menses, and overproduction or underproduction of urine. Pertinent diagnoses include diabetes, interstitial cystitis, urinary tract infection, dietary ketoacidosis, and intrinsic renal disease and renal failure.

Musculoskeletal

The most common symptoms involving the immune system, connective tissues, and joints are fever, rash, joint pain, bone fracture, morning stiffness, soft tissue swelling, low back pain, and muscle pain or weakness. Some of the more common musculoskeletal diagnoses include gout, scleroderma, Reiter's syndrome, rheumatoid arthritis, osteoarthritis, chronic fatigue syndrome, juvenile rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus.

Integumentary

The integumentary system involves disorders that affect the skin, hair, and nails. Common symptoms include the presentation of a rash, skin lesion or nodule, skin itching or pain, skin discoloration, and loss or new growth of hair. Common diagnoses include eczema, psoriasis, skin cancer, acne rosacea, alopecia, vitiligo, allergic dermatitis, and infection (i.e., herpes simplex or zoster).

Neurologic

The patient should note any alteration or loss of senses, including sight, hearing, smell, taste, or touch. In addition, any alteration or loss of sensory or motor skills, as well as memory or recall, should be noted. Pertinent neurologic diagnoses include tumors, stroke, seizures, epilepsy, Alzheimer's disease, Huntington's disease, multiple sclerosis, myasthenia gravis, pseudotumor cerebri, and amyotrophic lateral sclerosis.

Psychiatric

Mental disorders can make history-taking more difficult because of possible communication problems. The most common psychiatric complaints and diagnoses include anxiety (attacks of palpitations, sweating, shaking and shortness of breath), phobias, stress, obsessive-compulsive disorder, depression, bipolar disorder, schizophrenia, and personality disorders. In addition, alcoholism and drug dependency may be noted here.

Endocrine

Common endocrine problems include pituitary disease, thyroid disease, pheochromocytoma, and diabetes mellitus. Significant symptoms include palpitations, weight changes, changes in hair and skin, emotional changes, and an increase in hunger, thirst, and urination.

Hematologic/Lymphatic

These conditions include cancer, blood disorders, and lymphatic problems. Common blood problems include the anemias and polycythemias. Lymph node swelling should be noted.

Allergic/Immunologic

Symptoms include fever, sneezing, coughing, skin rashes, throat swelling, and sudden onset of itching.

GENERAL HEALTH HISTORY

The general health history is an amplification of the review of systems. In general, the most significant and common systemic problems are noted here. These problems include asthma, thyroid disease, systemic hypertension, diabetes mellitus, and a history of myocardial infarction and stroke. The present status of each diagnosis should be noted with the name of the treating physician. The name of the patient's primary medical physician and the date of her last physical should be noted in this section.

MEDICATIONS

All medications, both systemic and ocular, should be noted in a clear, concise manner. The notes should include the proper spelling of the medications (to avoid errors), the dosage, its frequency, and refills left. Any side effects of the medications should be noted.

SOCIAL HISTORY

The patient's driving history, which is a particularly important reason for the patient to have an eye examination, should be included. In addition, the patient should be honest about use of alcohol, tobacco, and recreational drugs. Any present or past treatment of sexually transmitted diseases should be noted here.

FAMILY HISTORY

The family medical history should include blood relatives with asthma, thyroid disease, systemic hypertension, diabetes mellitus, and history of vascular disease, heart attack or stroke.

The family ocular history should include blood relatives with glaucoma and age-related macular degeneration.

HISTORY CHECKLIST

In practice, the history can be a challenge to doctors who wish to efficiently examine the patient in a reasonable amount of time. To expedite the process, many offices give patients a checklist history that lists pertinent questions in a "yes" or "no" format.

The checklist has several advantages. It is efficient, because the patient fills out the history while waiting to be called back for the examination. The list is as thorough as necessary to meet the requirements of the office and general medical and optometry standards. The patient can slowly and correctly answer a series of questions in a non-intimidating setting. It is an unemotional way to gather sensitive medical and social information such as a history of drug abuse or sexually transmitted diseases. The list is probably the best way to ask a female patient whether she is pregnant, and also allows the examiner to review the history before greeting the patient, thus sensitizing the doctor to the patient's situation. For example, if the history indicates that a patient has a transmittable infection, the examiner can wear appropriate barrier protection.

The checklist history has some disadvantages. For the illiterate, elderly, or non-English-speaking patient, a checklist history can be intimidating if no family or friend is present to help the patient. The checklist may omit relevant questions or not focus on the area of concern to the patient. The list may not allow the patient to expand on a complaint. The checklist is impersonal and does not promote doctor-patient bonding. The examiner must take time to thoroughly review the checklist and then expand on important issues. The optometrist must use this time to forge the doctor-patient relationship.

SUMMARY

The history enables the optometrist to focus on pertinent tests and directs the course of the examination. Perhaps most importantly, the history helps the doctor to develop a personal connection with the patient.

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CHAPTER 2

The Physical Examination

CHAPTER OUTLINE

This chapter focuses on the art and science of the physical examination. An appreciation of clinical medicine is impossible without a sensitive understanding of the history, techniques, utility, and limitations of physical diagnosis.

To detect disease, the earliest clinicians relied entirely on their observations of patients. Physical diagnosis advanced with refinements in the techniques of palpation and percussion. The introduction of instruments for auscultation allowed clinicians to evaluate sounds produced by the internal organs (Figure 2-1).

The techniques of observation, palpation, percussion, and auscultation provide the framework necessary to achieve the primary goals of the physical examination. The first goal is to provide the initial basis for making decisions regarding laboratory and radiologic testing. The second goal is to facilitate the doctor-patient relationship. Finally, the examination provides important baseline information.

To master those aspects of the physical examination that are integral to the optometric practice, the student must learn and perform the techniques in the clinical setting. Only through repeated exposure to its methods and instrumentation can physical diagnosis as an art and discipline be appreciated and applied.

As science and medicine progress in complexity, the examination too often becomes impersonal. The physical examination encompasses the patient's physical and emotional pain. The examination should be carried out with sensitivity and compassion.

OFFICE SANITATION

The presence of multiple patients in the optometry office increases the risk of contagious diseases. Our patients act as reservoirs for such pathogens, and disease can spread unseen among clinicians, support staff, and other patients. Patients with systemic infections such as tuberculosis, hepatitis, and HIV-AIDS, as well as topical disease such as epidemic keratoconjunctivitis, place the entire optometry office at risk.

The optometrist must ensure as much as possible that the office is not a source of infection. To this end, appropriate cleaning and sterilization protocols can help keep the office environment healthy.

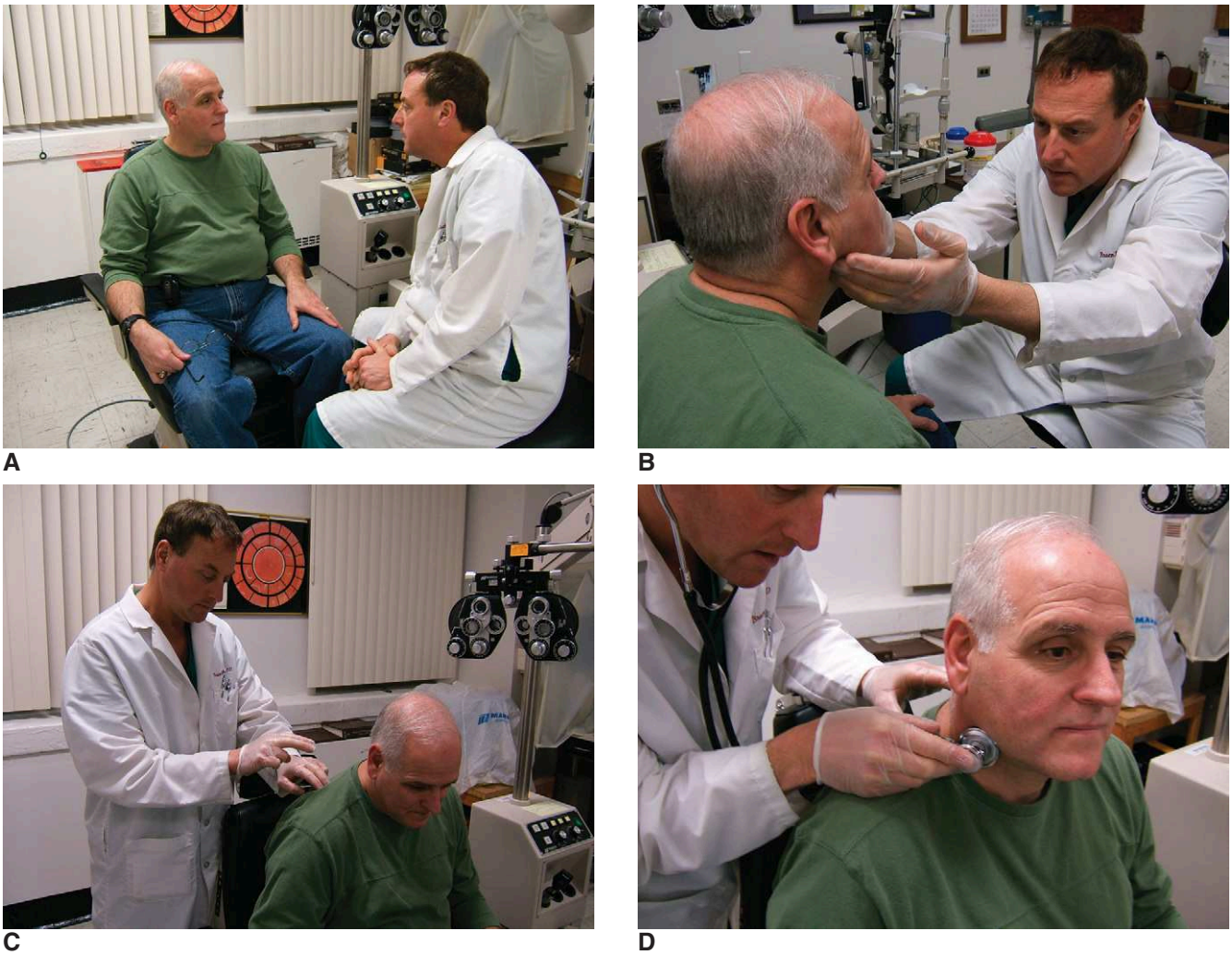


FIGURE 2-1 ■ **A,** Observation of the patient. The patient is inspected for general appearance, any asymmetry, posture, gait, and speech problems, and nutritional state. **B,** Palpation of the patient: The tactile sense is used to feel for masses, underlying abnormalities, and abnormal heart impulses. **C,** Percussion of the patient: A sound is produced by underlying structures when a sharp blow is delivered to an overlying site on the skin. This sound is evaluated to identify various problems in the underlying structures. **D,** Auscultation of the patient: Sounds produced by underlying organ systems are heard with the aid of the stethoscope.

All surfaces exposed to the constant flow of patients should be cleaned on a daily basis. Those areas most frequently touched by patients should be cleaned frequently. The pens used by patients to sign forms should not be shared by the support staff, and all writing utensils should be cleaned daily.

Patient's hands are a significant source of contagions, so it may be appropriate for the front desk to offer every patient, particularly children, a premoistened towelette to clean the hands. These items can be purchased in bulk supply to reduce the overhead cost, and should be hypoallergenic and nonfragranced.

A common source of pathogenic spread is the optometry equipment. All environmental surfaces that patients come in contact with should be wiped down with an appropriate cleaning agent that will not denature the material of the equipment. Staff should clean and dry the chinrest and headrest of the slit lamp before each examination. This practice will reassure the patient that the office follows sanitary protocols.

All hand-held instruments, such as ophthalmoscopes, retinoscopes, muscle lights, and occluders, should be wiped down daily. Hand-held cards, such as plastic Amsler grids, and color testing and stereo booklets, should be wiped down at least weekly.

Other environmental surfaces at risk include the phoropter, hand-held slit-lamp lenses, and the chin and headrests of keratometers, automated perimeters, the Heidelberg retinal tomograph (HRT), and the GDx nerve fiber analyzer (GDx) units and automated refractors.

The Goldmann tonometer tip should receive special attention, and staff should sterilize it before each examination by placing it in a 1:1000 solution of bleach

for a minimum of 15 minutes. In the busy practice, 2 tonotips alternately soaking can provide a ready-to-use Goldmann tonometer tip every 7½ minutes. Wiping the tonotip with alcohol or washing it with soap and water between examinations provides inadequate disinfection because some pathogens can survive this technique.

BARRIER PRECAUTIONS

Hand washing remains the single most effective way to decrease the spread of disease in the office environment. The clinician's hands should be washed with soap before each examination, preferably in front of the patient for reassurance. Most patients greatly appreciate this practice and it strengthens the doctor-patient bond. A recent study indicated that neckties worn by doctors are a source of infectious agents. Ties often come into contact with multiple patients, and are rarely cleaned. To avoid contamination, the physician can secure the tie under a lab coat, frequently clean the tie, or (preferably) not wear a tie.

Clearly defined procedures are necessary to ensure the safety of health care workers. Of particular concern to optometrists are HIV-AIDS, hepatitis, and tuberculosis. The Centers for Disease Control and Prevention and Occupational Safety and Health Administration have established precautionary guidelines for health care workers who may be exposed to infectious materials or body fluids.

Gloves should be used when examining any patient with HIV-AIDS and any form of hepatitis (even if treated and resolved). In addition, gloves should be used when examining any patient with a topical exudative or pustular weeping from the eye. Gloves should be used when appropriating samples for conjunctival culturing and sensitivities. All gloves must be disposed of in an appropriate disposal container.

Masks should be used in cases of active tuberculosis with a coughing patient. If significant coughing is present, it is appropriate for the examiner to ask the patient to wear a mask to prevent infection of an unprotected staff member or patient. Cases of treated and resolved tuberculosis do not require the examiner to wear a mask.

When examining a patient with an active varicella-zoster outbreak, any optometrist at risk (those who have never had chickenpox and those who have not received the varicella vaccine) should wear both a mask and gloves. A pregnant optometrist who has never had chickenpox and is not vaccinated should never examine a patient with an active varicella outbreak, even with appropriate barrier precautions, because of the risk of spread of the virus to the fetus. For this reason, female optometrists of child-bearing age should strongly consider receiving the varicella vaccine if they test negative for varicella antibodies. Eye protection is recommended in the optometry office if the possibility exists of splattering or aerosolization of body fluids.

All sharp instruments, such as disposable needles used to remove corneal foreign bodies or injections, should be handled with the utmost care. These items should never be recapped after usage, and should be disposed of in a clearly marked puncture-resistant (sharps) container. All optometrists who have direct contact with patients should complete the Hepatitis B vaccine series. It may be advisable for the optometrist to be tested for immunity first.

The hospital-based optometrist who is to examine a patient in isolation or is on special precautions should contact the institution's infection control manual for guidelines concerning restrictions on entry into the room. In addition, the examiner may be required to wear protective attire, such as a gown, to enter the room.

Barrier precautions are used to protect the patient, examiner, office environment, and other patients, although the majority of patient encounters require no barrier precautions. When in doubt, it is appropriate to overreact. The examiner can truly never be too cautious.

BASIC PROCEDURES

The goal of the physical examination is to obtain valid information concerning the health of the optometry patient. The ocular findings may affect the ultimate general health assessment (for instance, a large refractive shift may indicate diabetes mellitus in an undiagnosed patient). Any systemic findings may likewise have ocular ramifications (for example, a child with uveitis is seen in the office with swollen knees and is ultimately tested for Lyme disease and juvenile rheumatoid arthritis).

Four primary skills are essential in performing an appropriate physical examination. These skills are observation, palpation, percussion, and auscultation. The physical examination requires detailed observation by the practitioner from the moment the patient is first greeted. The examiner should evaluate the general appearance of the patient with regard to posture, alertness, and nutritional state. Any asymmetry of the body should be noted, inspected, and evaluated. Any asymmetry of the eyes, for example, is significant. Unilateral ptosis, a drooping of one of the upper eyelids, may be a sign of Horner's syndrome. If ptosis occurs with a fourth-nerve palsy, an immediate neurology consult with imaging to rule out an intracranial lesion is mandatory. Unilateral ptosis may be the result of a retrobulbar space-occupying lesion, and unilateral lid retraction may occur in Graves' disease. Anisocoria, an

inequality in pupil sizes, may be caused by sympathetic or parasympathetic lesions.

After the initial observation, the examiner should touch the patient's skin, a procedure known as palpation. Palpation of the body permits the examiner to assess any irregularity, enlargement, hardness, or heat associated with inflammation. To perform palpation, the clinician uses touch to evaluate the characteristics of an internal organ system. Most often the fingers and the palms of the hand are used because these are exquisitely sensitive detectors of underlying pressure and contour gradients. Palpation also facilitates a level of intimacy that encourages the development of the complex doctor/patient relationship (Figure 2-2).

The eyes are delicate and sensitive in many patients. Extraordinary care should be taken by the examiner in palpating the ocular and paraocular area. The examiner should perform crucial ocular palpation, including tactile judgment of proptosis, by placing the base of both forefingers of each hand against the closed lids of the patient's eyes. Palpation of the globes by the tips of the forefingers can help the clinician estimate intraocular pressures in patients who are not suitable to applanation or noncontact tonometry. In addition, palpation of the preauricular lymph nodes, as well as the nodes of the neck, may help in the diagnosis of viral conjunctivitis.

The optometrist does not need to palpate below the clavicle. A swollen preauricular lymph node in the context of a viral conjunctivitis is managed in the optometry office. Swollen and perhaps painful neck masses must be referred to the patient's primary care physician (PCP).

The examiner performs percussion by striking an area of the body to produce and evaluate the resulting sound. Percussion provides information about the size of an underlying organ, the presence of fluid in a normally air-filled cavity, and the presence of excessive dilatation caused by trapped air. To perform percussion, the clinician's left middle finger is placed firmly against the patient's body. The tip of the right middle finger is then struck against the left middle finger to produce the resulting sound (Figures 2-3 and 2-4).

Each organ produces a characteristic sound that results from the shock wave of the percussion as it passes through various tissues. Changes in the organ's size, density, or tissue composition result in characteristic changes in the sound produced. As the clinician gains experience with this skill, valuable predictions can be made concerning the health of an organ system.

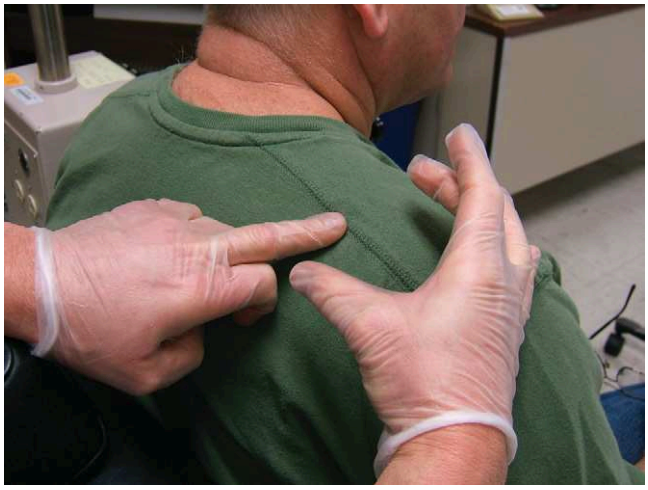


FIGURE 2-3 ■ Percussion. The examiner's left middle finger is placed over the site to be examined and pressed firmly on the skin.

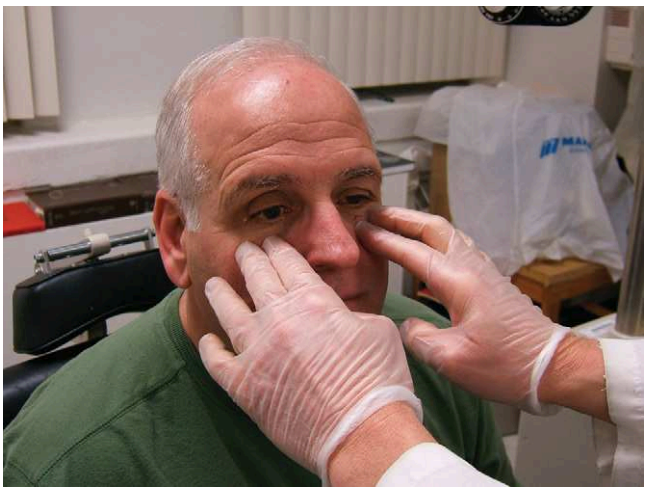


FIGURE 2-2 ■ Palpation. Small areas of skin or underlying masses may be palpated by use of one or two fingers moved in a circular pattern. Large masses are palpated with all the fingers or with the palm.

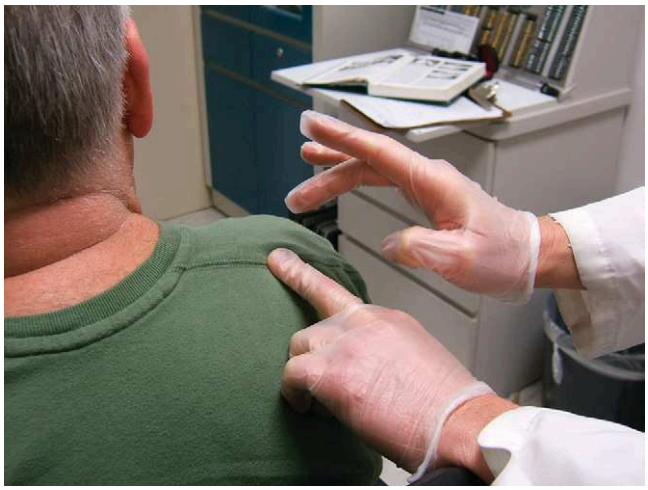


FIGURE 2-4 ■ Percussion. The examiner's right middle finger sharply strikes the left middle finger. The resulting sound is evaluated by the examiner.

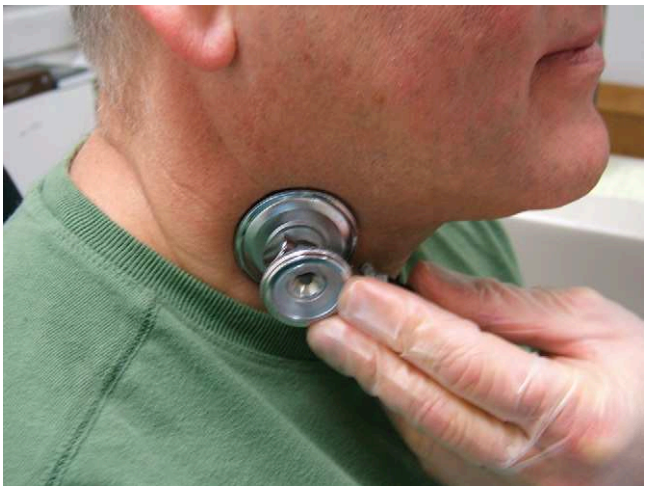


FIGURE 2-5 ■ Auscultation of the carotid artery. The diaphragm of the stethoscope is used on the patient, who is sitting or supine. The patient's head is turned away from the stethoscope and the patient holds his breath. The examiner listens to the carotid artery just above the clavicle, on the center of the neck, and just under the angle of the jaw.

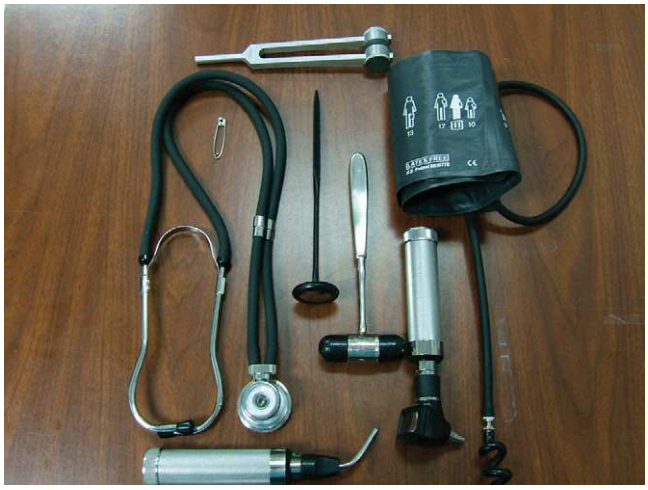
Percussion need not be performed around the eyes or head. Most often, the physician will percuss internal organs, including the lungs to rule out collapse, and the abdomen to detect bladder distention.

With the addition of simple yet refined instruments, such as the stethoscope, auscultation has become an essential part of the physical examination. Listening with the stethoscope allows the examiner to detect adventitious lung sounds that suggest pneumonia or heart failure (see Chapter 9). Auscultation is also used to evaluate the heart for murmurs that suggest valvular dysfunction. Of particular interest to the optometrist is the use of auscultation to detect the presence of bruits caused by narrowing of blood vessels secondary to atherosclerosis. The carotid bruit is a significant finding in a patient experiencing the visual symptoms associated with a transient ischemic attack (TIA) (Figure 2-5).

THE INSTRUMENTS

The four cardinal skills of the physical examination are enhanced by the use of other medical instruments. The instruments used to examine the ears, nose, throat, larynx, esophagus, stomach, rectum, colon, and joints fall under the category of endoscopes. These scopes enable the examiner to look within the body through natural or surgically created holes. Simpler equipment is also used to help perform various tests. Refinements in these instruments have accelerated as each decade passes, but the decision to use this technology is costly, and the diagnosis ultimately depends on the human skills of history taking and physical examination.

Mandatory equipment for the routine physical examination includes the stethoscope for auscultation, the penlight for specific illumination and pupil testing, the otoscope for the ear examination, the ophthalmoscope for the eye examination, safety pins for sensory testing, a 128-Hz tuning fork for audition, and a reflex hammer for deep tendon reflex testing. Other equipment includes a nasal speculum and illuminator, sphygmomanometer for blood pressure measurement, tongue depressors, and cotton-tipped applicators. Barrier protection for the clinician and patient includes gloves, mask, and eye protection (Figure 2-6).



A

B

FIGURE 2-6 ■ **A,** The instruments of the physical examination. Included here are the stethoscope, penlight, otoscope, ophthalmoscope, safety pins, tuning fork, reflex hammer, nasal illuminator, sphygmomanometer, tongue depressor, and cotton-tipped applicators. **B,** Barrier protection for doctor and patient. Included here are mask and gloves.

THE LANGUAGE OF THE PHYSICAL EXAMINATION

Language is an important element of the physical examination. Although language is a means of communication, it can also be a source of confusion. Clinicians communicating with patients during the physical examination must be aware of the need to interpret medical terminology so that the patient understands it (Table 2-1). The language of the physical examination includes eponyms and colorful descriptives that can both frighten and confuse patients. Although eponyms bestow honor on clinicians who have made observations and disseminated them to their peers, they have no value in terms of description. In general, description is preferable to use of eponyms.

The sheer number of fascinating eponyms associated with the eye indicates how central the eye has been in the development of the physical examination. A few of the ocular signs of systemic disease that are denoted by eponyms include Adie's tonic pupil, Brushfield's spots of the iris, the Kayser-Fleischer corneal ring, Hollenhorst plaques of the retinal vasculature, and Homer's syndrome.

A myriad of eponyms denote lid abnormalities associated with hyperthyroidism (see Chapter 12), such as von Graefe lid lag, the infrequent blinking known as Stellwag's sign, the tremor of the closed lids known as Rosenbach's sign, and the lag of the lower lid during globe elevation known as Griffith's sign. A similar litany of famous names is attached to other important signs in the physical examination.

The physical examination sometimes uses colorful language to help describe a clinical observation. Numerous examples are associated with the eye. The copper-wiring associated with arteriosclerotic change in the retina, the nerve infarctions known as cotton-wool spots, and the mutton fat precipitates of the cornea seen in granulomatous uveitis all illustrate colorful and descriptive language.

Similarly, sputum has been described with such terms as "rusty," "currant jelly," or "prune juice." Each description indicates a certain type of infectious organism. The characteristic skin rash of chickenpox or its reactivation as herpes zoster is referred to as "dew drops on a petal." In patients with cirrhosis of the liver, the dilated veins that may form around the umbilicus have been called the caput Medusa, named for the mythological goddess who had snakes in place of hair. These poetic descriptions all help visualization of the abnormalities being described.

TABLE 2-1 SYSTEM-BY-SYSTEM USEFUL VOCABULARY

ORGAN OR SYSTEM	MEDICAL TERM	DEFINITION
Ear	Audiometer	A device that measures hearing
	Presbycusis	Hearing loss with age
	Otitis	Inflammation of the ear
	Phonasthenia	Voice weakness
Mouth	Stomatitis	Inflammation of the mouth
Chest	Bronchitis	Inflammation of the bronchus
	Dyspnea	Shortness of breath or difficulty breathing
	Hemoptysis	Coughing up blood
	Apnea	Temporary cessation of respiration
Heart	Bradycardia	Slow heart rate
	Tachycardia	Fast heart rate
	Cardiomegaly	Heart enlargement
Breast	Gynecomastia	Excessive male breast development
	Lactation	Milk secretion
	Mammogram	X-ray of breast
	Mastitis	Inflammation of the breast
Abdomen	Colitis	Inflammation of intestine
	Cholecystitis	Inflammation of gallbladder
Urogenital system	Nephropathy	Kidney disease
	Pyelogram	X-ray of kidney
	Metrorrhagia	Uterine bleeding
	Hematuria	Red blood cells in urine
	Pyuria	White blood cells in urine
Musculoskeletal system	Arthritis	Inflammation of joint
	Myopathy	Muscle disease
	Scoliosis	Lateral deviation of the spine
Nervous system	Dysesthesia	Abnormal sensation
	Agnosia	Loss of recognition of sensory stimuli
	Paresis	Weakness
	Neuropathy	Nerve damage
	Aphasia	Inability to speak

VITAL SIGNS

The vital signs include measurements of the patient's temperature, pulse, blood pressure, respiratory rate, height, and weight. Normal body temperature is defined as 98.6° F, but a patient's temperature may be slightly higher or lower. A temperature elevation may be a sign of disease, indicating a reaction of the body to infection. Circadian variation sometimes causes people who are ill to have a normal temperature in the morning and an elevated temperature later in the day. Fevers tend to be highest at night (Figure 2-7). Any patient coming to the optometrist's office with signs of systemic inflammation should have an oral temperature reading.

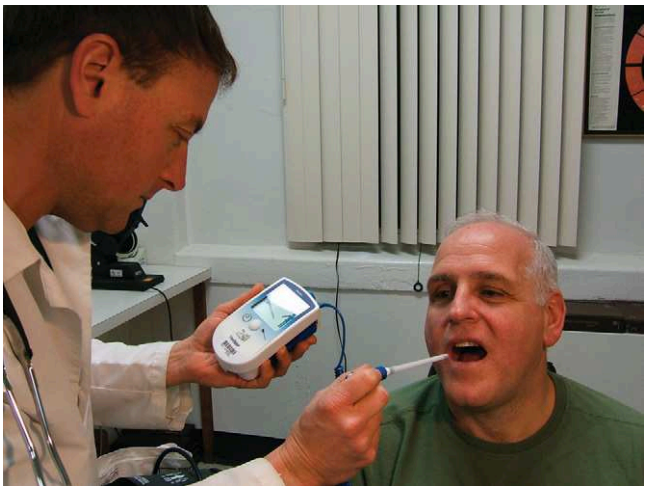


FIGURE 2-7 ■ Measuring the patient's temperature. Use of an oral thermometer can determine a patient's temperature. A sterile thermometer is shaken so that its initial reading is well below 98.6° F. It is placed beneath the tongue of a patient and read in 1 minute.

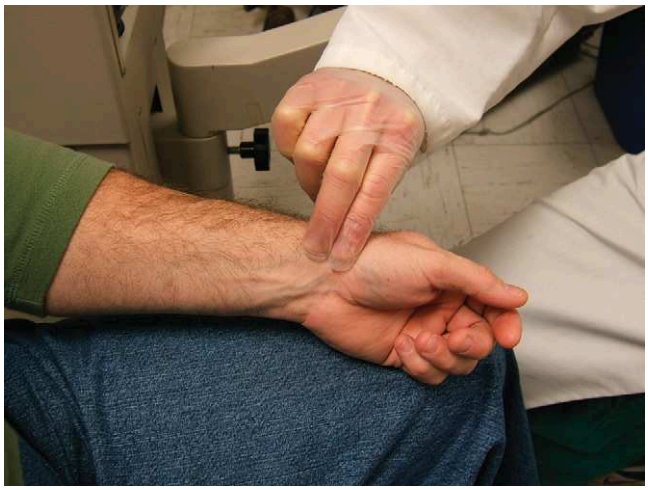


FIGURE 2-8 ■ Measuring the patient's pulse. The index finger, middle finger, and fourth finger are placed over the radial artery (wrist pulse) below the base of the patient's thumb. The pulse is counted for 30 seconds and multiplied by 2 to get a pulse rate for 1 minute.

The pulse is assessed for rate and regularity. A normal rate is 50 to 70 ppm, but pulse rate may be lower in a young athlete or in an elderly heart patient with a disease of the conduction system. Elevated pulse rate occurs with increased respiration; this condition is known as normal sinus arrhythmia. Premature beats may be perceived as early, extra, or skipped beats, because a long pause follows the early beat. The pulse may be rapidly irregularly irregular, as with atrial fibrillation (Figure 2-8). All optometric patients can be evaluated for pulse rate. If bradycardia (slow rate) or an irregular heartbeat is found in a glaucoma patient, the examiner should call the family physician before prescribing a beta-blocker for glaucoma treatment.

The clinician measures blood pressure with a sphygmomanometer and stethoscope by auscultating and evaluating changes in the pulse as pressure is released from the cuff (Figure 2-9). The first heart sound heard as pressure is released is the systolic pressure, or the pressure that is maximally achieved when the heart pumps. Continued auscultation reveals disappearance of the pulse, which represents the diastolic pressure, or the pressure during the filling phase of the heart. Blood pressure is arbitrarily judged to be high based on an accepted normal reading of 140/90 mm Hg or less, but blood pressure must be interpreted in the context of age, the relative excitement of the patient, and measurement limitations. For example, a very thick arm may produce an artificially elevated blood pressure, and the clinician must use a wide thigh cuff to determine pressure accurately. Blood pressure readings are mandatory for any optometric patient who is to be dilated with phenylephrine, because this sympathomimetic can raise systemic blood pressure temporarily.

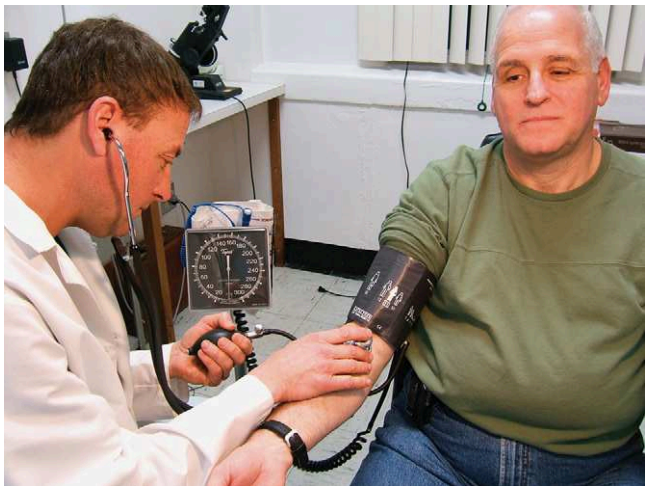


FIGURE 2-9 ■ Measuring the patient's blood pressure. The sphygmomanometer provides an indirect measurement of blood pressure by detecting the appearance and disappearance of the Korotkoff sounds over an artery compressed by an air-filled bladder. Evaluation of both arms may be necessary.

Respiratory rate can be a clue to underlying breathing difficulties. In very ill patients, various types of respiratory patterns may indicate metabolic abnormalities or levels of coma. Dyspnea (difficulty in breathing) in a glaucoma patient may preclude the use of beta-blockers, because these drugs can exacerbate asthma.

Height and weight are important measurements. Changes in weight must be measured and ultimately explained. Significant weight gain is associated with pseudotumor cerebri, which causes elevated intracranial pressure. Headache and reduced visual acuity can accompany the papilledema that is secondary to elevated intracranial pressure. A significant finding in these

patients is often a history of recent weight gain. Height and weight can easily be measured in the optometrist's office, or recent readings can be obtained with the patient's permission from the family physician.

EXAMINATION OF THE SKIN

The skin, or integument, is the outer aspect or covering of the body and is the first system to be examined. The optometric evaluation of the skin is usually limited to the head, neck, arms, and hands. The detection of possible skin cancers is a critical element of this part of the physical examination. Skin cancers are detected by observation and confirmed by removal of tissue and subsequent examination under the microscope (biopsy). The patient may present with symptoms of skin disease, including pruritus (itching), a rash, and changes in skin, hair, or nails.

Examination of the facial skin can be useful to determine significant disease. Pigmented lesions such as seborrheic keratoses must be differentiated from melanoma. The characteristics of melanoma include irregular borders and surface details and changes in color. The inflamed tissue is red but may become white from necrosis or turn blue from deep invasion of the melanoma. Pigmented lesions should always be observed, measured, described, documented with drawings or photographs.

Many clinical diagnoses derive from observation of the facial skin. Skin coloring may be a risk factor in the development of skin cancer. The clinician should therefore caution a fair-skinned patient about the importance of sunscreen. Areas of redness and roughness, known as actinic keratoses, or sun damage, should be treated for cosmetic reasons and for their tendency to become malignant.

Thinning of the skin with visible vessels, called telangiectasias, may be a normal variation or the result of sun damage. Telangiectasias may also be spider angiomas, which when compressed seem to fill from the center with spider-like tentacles. Spider angiomas may indicate estrogen excess or may be related to a specific skin disease like acne rosacea.

Small papules or pimples may be normal variations or may require a referral to another physician for the treatment of acne. Blackheads around the eyes in older patients can be treated for cosmetic purposes.

The color of the facial skin is changed by the presence of some diseases. For example, pallor of the skin may indicate anemia, and a yellowing complexion may suggest underlying jaundice or liver disease.

Skin Terminology

Familiarity with the terminology used to describe skin lesions is important (Table 2-2). Localized changes in the color of usually flat red lesions of 1 cm or less in size are called macules (for example, freckles). Elevated areas less than 1 cm in diameter are called *papules* (for example, acne). Rashes that have a flat, red area are called maculopapular. A patch is a macule greater than 1 cm in diameter (for example, vitiligo).

TABLE 2-2 BENIGN VS. MALIGNANT SKIN CHARACTERISTICS

CHARACTERISTIC	BENIGN	MALIGNANT
Height	Flat	Elevated
Growth	Stable	Growth
Color	Similar to surroundings	Different from surroundings
Function	No disruption	Disruption
Blood vessels	Absent	Present
Borders	Sharp	Indistinct
Satellites	Not present	Present
Bleeding	No	Yes
Time	Long-standing	Recent

Raised areas greater than 1 cm are referred to as nodules. Plaques have a large surface area in relation to their height. For example, the skin lesion present in psoriasis is a scaling plaque. Plaques that are yellow are often called xanthomas, or they may be small seborrheic cysts. Xanthomas on the eyelid are known as xanthelasma and may be a sign of elevated cholesterol.

An elevation of the skin with a clear fluid accumulation of less than 1 cm just beneath the upper layer is called a vesicle. A cold sore is a type of vesicle. Accumulations of clear fluid larger than 1 cm are called bullae. Vesicles and bullae are clear because their fluid is not infected. An accumulation of fluid that is thicker, more opaque, and yellow, green, or orange is called a pustule and may indicate active infection.

In summary, the skin examination is divided into two parts. The first part consists of detection of pruritus or changes in skin color, hair, and nails. The second part consists of inspection and palpation of the hair, nails, and skin of the neck, face, back, chest, abdomen, arms, and legs. All lesions should be described and documented and clinicopathologic correlations made (see Chapter 16). Any suspicious skin lesion found during the optometric examination should be documented and the patient monitored or referred to the family physician or a dermatologist.

Review of Skin Symptoms

The appearance of a new rash or skin lesion on the head or neck should prompt an investigation. The optometrist should ascertain from the patient the specific time of onset and any changes in the rash over time.

Associated characteristics such as elevation, blistering, itching, tenderness, and numbness should be identified. New areas of skin involvement are significant.

The examiner should ask whether close family members have similar rashes. Patients should reveal whether this has happened before, if so, how it was treated, and whether it is currently being treated.

Overall skin color may change because of the presence of systemic disease, as in cases of jaundice, which produces a yellow skin tone caused by liver problems. Localized skin color changes around the head and neck may be to the result of aging, neoplastic changes, or medications.

Generalized itching, or pruritus, may be caused by biliary cirrhosis, or cancers, such as pancreatic or lymphoma. Localized pruritus is often associated with a contact dermatitis rash, as in cases of poison ivy, or viral infection, as in a herpes zoster outbreak. Changes in hair density and texture may be related to systemic diseases, diet and medications. Ovarian, adrenal, and pituitary tumors may cause significant changes in hair texture.

EXAMINATION OF THE EYE

After the skin evaluation, the clinician examines the eyes. Significant eye symptoms include loss of visual acuity, field loss, eye pain, redness, diplopia, tearing, discharge, or trauma. This examination includes a visual acuity measurement, confrontational visual field testing, pupil testing, extraocular muscle motility assessment, and fundus evaluation with an ophthalmoscope. The skin around the eyes is checked carefully for any lesions, such as basal cell carcinoma. Basal cell lesions can appear as small, red, or bleeding sores found especially around the eyes and bridge of the nose. Last, the cornea is evaluated for pterygium, and the lid is everted to look for conjunctival cysts, lumps, or changes in color. An in-depth discussion of the ocular portion of the physical examination is omitted in deference to the reader's expertise.

EXAMINATION OF THE NOSE

Significant nasal symptoms include frequent nosebleeds, nasal discharge, nasal obstruction, sinus infection, and hay fever. Frequent nosebleeds, or epistaxis, are usually caused by nose picking, but malignancy must be considered. Examination of the nose requires inspection of its outer detail as well as its internal structures, which are viewed with the assistance of a nasal illuminator (Figure 2-10). Examination of the nasal mucosa indicates whether it is swollen and pale (as in allergic rhinitis), swollen and red (as in a viral rhinitis), and dry and cracking (from environmental changes such as dryness). By obtaining a nasal illuminator head for the ophthalmoscope, the optometrist can easily perform this examination. A practitioner can often discover clues to illicit drug use, such as punctate ulcerations from cocaine or actual perforation of the nasal septum from a vasoconstricting illicit drug. Nasal tumors can be detected through careful observation.

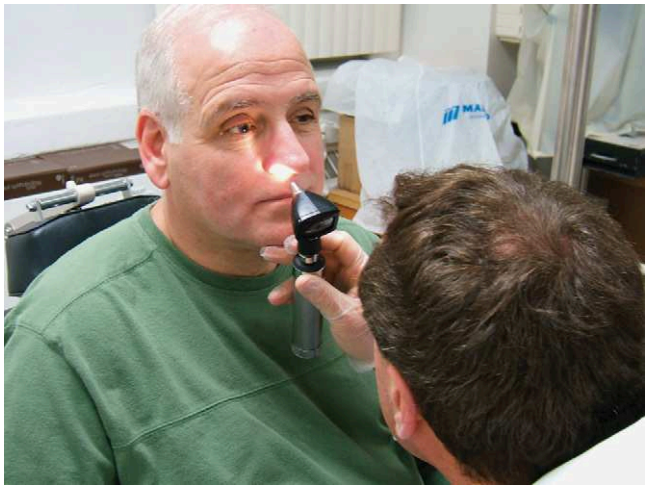


FIGURE 2-10 ■ The nasal illuminator. The nasal illuminator aids in the evaluation of the nose.

A bloody discharge is caused by rupture of the superficial mucosal vessels. Known as epistaxis, this discharge may result from trauma, bleeding disorders, systemic hypertension, chronic sinusitis, or malignancy. Inflammation of the nasal mucosa, or rhinitis, may be allergic or non-allergic in etiology. Symptoms include nasal obstruction with itchiness and sneezing associated with a clear, watery nasal discharge.

EXAMINATION OF THE MOUTH

Significant complaints of oral cavity problems include bleeding gums, frequent sore throats, dysphonia (hoarseness, voice changes), and postnasal drip. Dysphagia, or difficulty swallowing, is a significant symptom of obstruction or neurologic problems. The oral cavity is examined with a light and a tongue depressor to allow visualization of all structures (Figure 2-11). The posterior pharynx and tonsils are examined for inflammation, infection, enlargement, and abnormal lesions that might be cancerous.

The underside of the tongue and the area between the teeth and the lips should be examined to identify premalignant or potentially malignant conditions. Normal variations, such as torus palatinus, a bony structure emanating from the hard palate, must be differentiated from more serious conditions. When anything abnormal is visualized—whether it is a lump, a bony prominence, a white plaque known as leukoplakia, or a red plaque known as erythroplakia—it should be palpated to provide a more complete description. Any abnormalities noted on the oral examination warrant a referral to the family physician or dentist.

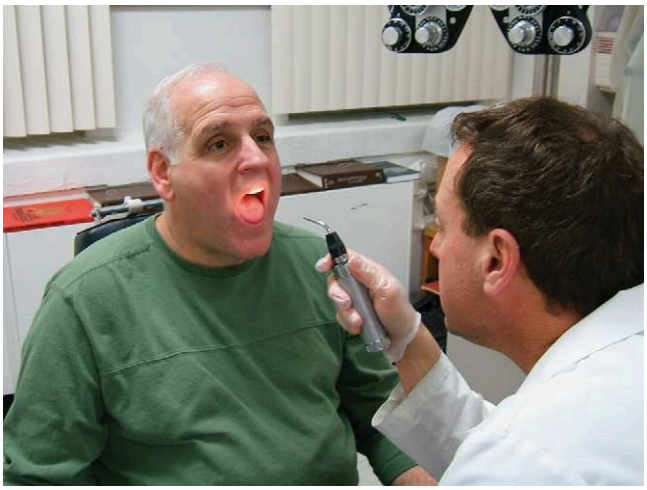


FIGURE 2-11 ■ Examination of the mouth. A penlight and optional tongue depressor are used to evaluate the teeth, gums, buccal mucosa, tongue, tonsils, uvula, and lips.

Pain in the teeth is most commonly a sign of underlying gum disease, or gingivitis. Patients who complain of tooth pain during physical exertion, however, may have chest pain from angina referred to their teeth. Oral ulceration may result from trauma, malignancy, or infections. For example, in all cases of uveitis the buccal mucosa must be explored for ulcers that may be related to Behçet's disease.

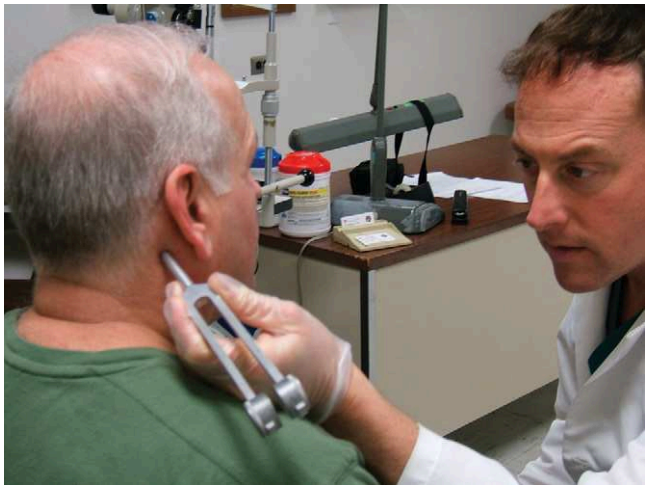
All patients with dry-eye syndrome should be asked about the presence of a dry mouth. This may occur in aging, Sjögren's syndrome, and in the use of certain medications. Oral examination may help to confirm trauma to the orbital floor with subsequent blow-out fracture. Because the inferior orbital contents prolapse downward through the fracture, an entrapped branch of the fifth cranial nerve may cause reduced sensation to part of the upper gum. First, the wooden end of a sterile cotton-tipped applicator is gently pressed against the gum behind the incisor ("eye tooth") on the uninvolved side. Next, the applicator is pressed into the gum behind the incisor tooth of the involved side. The patient is asked to compare the sensation on either side. If the gum on the side of the orbital trauma is numb when compared with the sensation on the uninvolved side, then a blow-out fracture is likely.

If the patient reveals an oral mass or bleeding in the history, he or she should be referred to his or her physician to evaluate for a possible trauma.

EXAMINATION OF THE EAR

Significant ear complaints include hearing loss, otorrhea (ear discharge), vertigo (dizziness), otalgia (pain), tinnitus (ringing in the ears) and ear infection. Examination of the ear requires observation of its external structures for abnormalities such as squamous cell carcinoma. The examiner then inspects the ear canal and drum with the assistance of an otoscope. Significant signs of inflammation include redness or swelling of the canal and drum and a loss of the drum light reflex, suggestive of fluid behind the drum. An excessive accumulation of cerumen (ear wax) can block the canal or press against the tympanic membrane and produce hearing loss.

Two hearing tests can easily be performed by the optometrist in the office. Both tests make use of a 512-Hz tuning fork. The Rinne test involves placement of a vibrating tuning fork on the mastoid sinus of the patient (Figure 2-12). The patient hears the sound by bone conduction. When the sound subsides, the patient signals the examiner, who then removes the fork and brings it to the opening of the patient's ear. The sound should still



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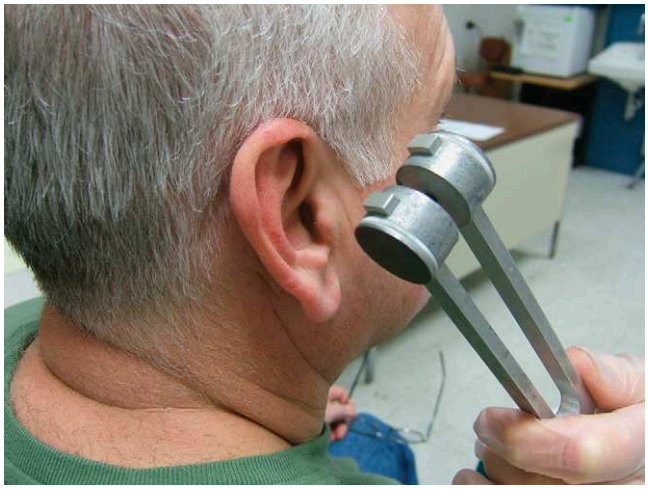

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FIGURE 2-12 ■ The Rinne auditory test. **A,** A vibrating tuning fork is placed on the mastoid process. **B,** When the patient no longer hears a sound, the tuning fork is removed and brought to the ear opening. The sound should continue to be audible to the patient.

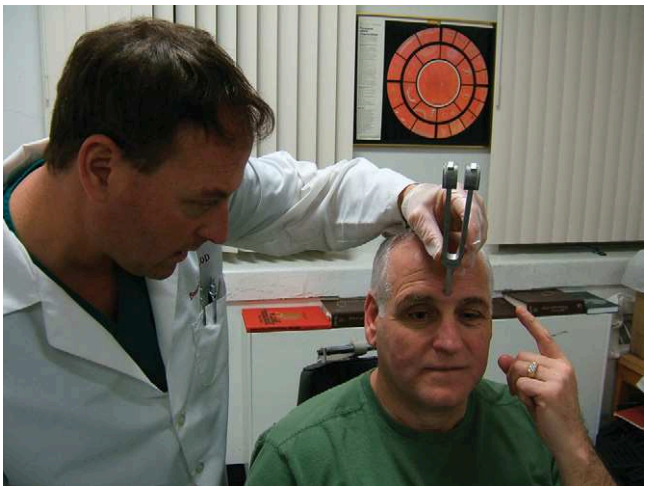


FIGURE 2-13 ■ The Weber test. A vibrating tuning fork is placed in the center of the patient's forehead. Normally the vibration sounds are equally loud to both ears. A conduction deficit lateralizes the sound to the affected side. A sensorineural deficit lateralizes the sound to the unaffected side.

be audible, because air conduction is superior to bone conduction. If the patient has a conductive hearing loss, then bone conduction, which bypasses the obstruction, will be superior to air conduction.

If the patient has a sensorineural deficit, then air conduction will be better than bone conduction because the middle ear amplifies the sound the same amount in both positions.

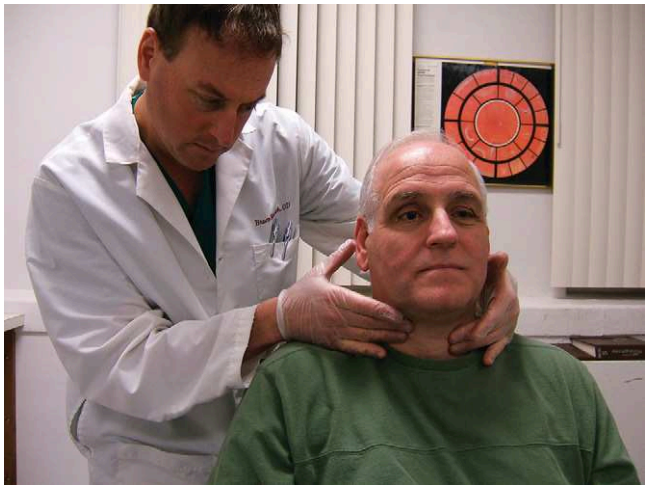
A second method, the Weber test, also makes use of a vibrating 512-Hz tuning fork. This time the tuning fork is placed on the center of the patient's forehead. The Weber test evaluates bone conduction between the ears. Normally, the patient hears a sound equally in both ears. If the sound is louder in one ear, that ear may have a conduction deficit. To prove this principle, plug one ear with a finger to produce a conduction deficit and hum softly. The sound seems louder in the occluded ear. Of course, if a sensorineural deficit is present in one ear, the sound is lateralized to the unaffected side (Figure 2-13).

EXAMINATION OF THE NECK

After examination of the head, eyes, ears, nose, and mouth, which requires primarily observational skills with the assistance of instruments, the clinician should focus on the neck. Significant presenting symptoms of neck problems include pain, goiter, tenderness, neck stiffness, and anomalous lumps. The multiple structures in the neck should be observed and carefully palpated.

First, the midline position of the trachea is confirmed by observation. Next, the neck is inspected for any asymmetry or visible abnormal lumps. An enlarged central lump is suggestive of an enlarged thyroid, or goiter. Lumps along the sides of the neck are suggestive of enlarged lymph nodes. Enlarged salivary glands can be observed and palpated under the chin. Dilation of the veins of the neck may suggest congestive heart failure.

Palpation of the neck is the most critical part of the examination. The examiner should palpate the thyroid and, if an enlarged thyroid is detected, ask the patient to swallow a sip of water. The act of swallowing allows the thyroid to move up and down, making it easier to palpate (Figure 2-14). The size, symmetry, and consistency



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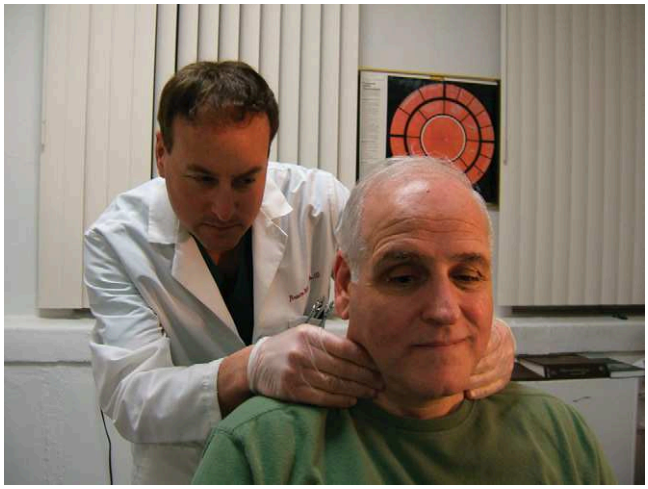

B

FIGURE 2-14 ■ Palpation of the thyroid. **A,** Anterior approach. The patient tilts his chin slightly to the right as the examiner grasps the right sternocleidomastoid muscle and displaces the larynx to the patient's right side by use of the examiner's left hand. The patient swallows and the right lobe of the thyroid is felt moving up and down against the examiner's right thumb and fingers. The process is reversed for the left lobe. **B,** Posterior approach. The examiner places both hands on the patient's sternocleidomastoid muscles. The left hand pushes the trachea to the right while the patient swallows. The right lobe is felt against the sternocleidomastoid muscle with the right hand. The process is reversed for the left lobe.

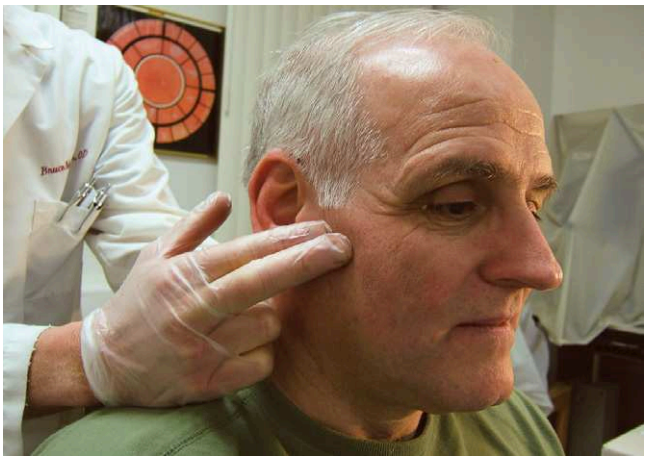

FIGURE 2-15 ■ Palpation of preauricular lymph node. The preauricular lymph node is found just in front of the ear where the jaw articulates with the cranium. This node may become enlarged and painful with viral conjunctivitis.

of the thyroid should be described. The optometrist should palpate the thyroid of any patient exhibiting signs of Graves' disease (see Chapter 12).

The lymph nodes should be described in the entire neck and head area. If inflammation of the eye is present, the optometrist should examine the preauricular lymph nodes, which are the major area of lymph drainage (Figure 2-15). Lymph nodes occur along the jugular vein in the neck, across the back (the posterior cervical lymph nodes), behind the ear, under the jawbone (the submandibular lymph nodes), and under the chin (the submental lymph nodes).

Any lymph node enlargement must be explained, because it is a key sign in many diseases. Such enlargement is usually the result of inflammation or infection, but lymph nodes that grow and become firm, hard, or irregular may indicate a lymph node tumor known as lymphoma. In other situations, a tumor arising elsewhere in the body can metastasize and cause enlarged and hardened lymph nodes.

Lymph nodes must be palpated in the supraclavicular area just above the clavicle. Lymph nodes below the clavicle are within the purview of the patient's PCP and if noted on history to be painful or palpable, a referral is mandatory. The patient's PCP will then palpate the lymph nodes in the axilla (armpit), and in the inguinal (groin) area. Although painful lymph nodes are often associated with inflammation or infection, painless lymph nodes can also be associated with malignant change.

AUSCULTATION OF THE CAROTID ARTERY

An important examination, auscultation of the carotid arteries involves listening for abnormal sounds suggestive of narrowing of the artery. Detection of these sounds, called bruits, sometimes requires a carotid work-up (Figure 2-16). Causes of carotid bruits include excessive blood flow (in a young person), transmission of a murmur from the heart, or narrowing of the carotid arteries. Any patient seen with the ocular symptoms of a transient ischemic attack warrants a carotid auscultation, because carotid plaques may occlude the ocular blood flow, causing sudden loss of vision. Usually these changes are monocular when they originate in the carotid artery. Whether or not the optometrist hears a bruit, the patient requires a carotid work-up by a vascular specialist as long as all other causes of the transient attack have been eliminated (see Chapter 6).

The carotid arteries are located lateral to the thyroid cartilage between the trachea and sternocleidomastoid muscle. Fatty accumulations of lipid, fibrin, and cholesterol may develop on the inner walls of the carotid artery. The formation of this thrombus may grow to eventually cause complete blockage, or stenosis, of the artery. Reduced blood perfusion to the brain leads to cerebral ischemia and possible stroke.

Alternatively, pieces of the carotid thrombus may break off and travel downstream to the vascular system of the eye or brain. These emboli may temporarily lodge in a blood vessel in the eye, causing transient, unilateral blackouts of vision. Likewise, the embolus may lodge in a cerebral vessel causing episodic and variable loss of neurological function. These TIAs, whether ocular or cerebral, indicate the increased risk of stroke. Even in the absence of symptoms, an ocular examination of the fundus may uncover Hollenhorst plaques located in the retinal arterial tree. These

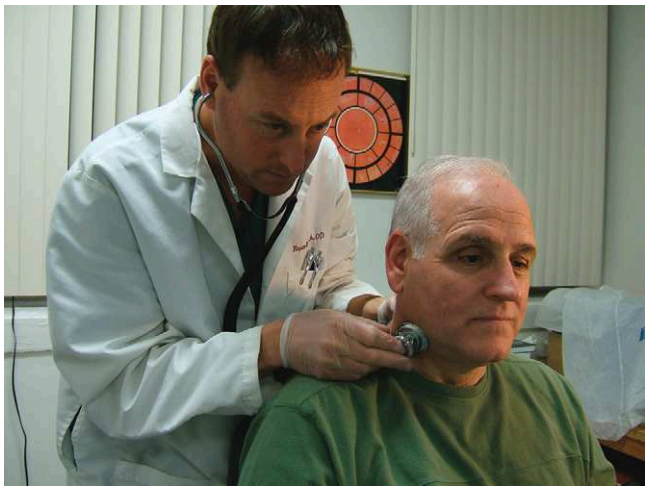

FIGURE 2-16 ■ Auscultation for carotid bruit. Thrombus development in the carotid artery causes the normally smooth and laminar blood flow to become disturbed and produce a "whooshing" sound heard between the two quick beats of the carotid pulse. Instead of the normal "*blub-dup, blub-dup*" the sound becomes "*blub-woosh-dup, blub-woosh-dup.*"

emboli, composed of fibrin, calcium, or cholesterol, may have originated in the carotid system.

A patient with a history of ocular or cerebral TIAs, or in whom plaques are found, must therefore have an evaluation of their carotid arteries. Normal blood flow through the carotid artery is laminar in nature and therefore fairly silent when auscultated. The sound generated by auscultation of the normal carotid artery consists of the beat of the heart as transmitted up the vascular tree. The sound is best mimicked as "*Blub-dup, blub-dup, blub-dup*."

The presence of a thrombus creates turbulence in the smooth flow of blood. This sound, or bruit, is heard between the quick beats of the heart. The sound thus auscultated is best mimicked as "*Blub-whoosh-dup, blub-whoosh-dup, blub-whoosh-dup*."

For auscultation of the carotid artery, the patient should ideally lie supine, but can be seated comfortably, and facing the examiner. Tight collars should be loosened. The patient should be instructed to turn his or her head slightly to the left, thus exposing the right carotid artery to the examiners' stethoscope. Because a bruit sounds like a rush of air, the patient should be asked to hold his or her breath during the test.

Either the flat head or the bell of the stethoscope can be used for examination. The head of the stethoscope is placed over the carotid artery just superior to the clavicle. The examiner asks the patient to hold his or her breath, and the carotid is auscultated during 4 or 5 beats of the heart. Next, the patient is asked to breathe and the head of the stethoscope is brought up to the middle of the neck. The process is then repeated. Finally, the head of the stethoscope is brought to the angle of the jaw and the carotid is once again auscultated. The process is repeated on the other carotid.

Detection of a carotid bruit mandates a carotid artery and cardiovascular work-up to search for thrombus and cardiovascular disease. On finding a bruit, the examiner should take a pen or indelible ink and circle the area of the bruit on the neck of the patient. Referral should be made within days to the patient's PCP for confirmation of the bruit and initiation of a vascular work-up. The circled area on the patient's neck should last until they see their PCP and serves as a visual queue as to the location of the bruit and will help the PCP localize the involved area. If the stethoscope is offset by just a short distance from the bruit, it may not be auscultated and the carotid thrombus may be missed.

Any patient with TIAs should have a carotid work-up even in the absence of a bruit. The work-up should be done because auscultation of the carotid arteries is at best a screening technique, and a carotid thrombus may not result in a bruit. In addition, the carotid artery must be more than 50% occluded for the bruit to be produced. But if the carotid is occluded by more than about 85%, the artery may be too narrow to produce a bruit. This circumstance yields a false-negative result.

The detection of a bruit also mandates a diligent search for Hollenhorst plaques in the retinal arterial trees of both eyes. This search is best conducted by a pupil dilation and use of a hand-held stereoscopic fundus lens at the slit lamp. The retinal arterial plaque will appear as a bright white, yellow, or gray mass lodged most commonly at the bifurcation of a retinal artery or arteriole. Blood may be seen distal to the plaque within the retinal vascular tree. When visualized through the binocular indirect ophthalmoscope head loop, the plaque will appear as a glistening white dot within a retinal arteriole.

The carotid artery should be palpated to gain information regarding poor blood flow and changes in the heart valves, but it is important never to palpate a carotid artery in which a bruit or thrombus has been discovered. Physical pressure on the plaque may cause it to dislodge and embolize.

EXAMINATION OF THE LUNGS

Patients with lung problems (see Chapter 9) may complaint of cough, chest pain, dyspnea (difficulty breathing or shortness of breath), sputum production, hemoptysis (coughing up blood), or a history of lung disease, such as asthma, emphysema, tuberculosis, or sarcoidosis. The clinician should examine the lungs by inspecting for abnormalities in symmetry, scoliosis (lateral curvature of the spine), and audible wheezes during inspiration or expiration.

After this evaluation, the examiner percusses the lung by pressing on the patient's chest or back with the middle finger of one hand and striking it with the middle finger of the other hand. A resonant note indicates hollowness produced by the presence of air. A dull note suggests fluid, which can accumulate in a patient with pneumonia or heart failure. An abnormal accumulation of fluid in the pleural sac is known as pleural effusion.

The stethoscope is then used to listen for abnormal lung sounds. In the healthy patient, the practitioner should be able to hear air coming into the lungs on inspiration and going out on expiration. If spasm of the bronchial tubes is present, the clinician may hear a wheeze suggestive of asthma. Fluid in the lungs produces a crackle, or rale, which is sometimes likened to the sound made by rubbing hair between two fingers. Louder variations of that sound are known as wheezes, or rhonchi. Rales and rhonchi suggest fluid, which may be caused by congestive heart failure or infection such as pneumonia. Sometimes sounds are heard that can be cleared by asking the patient to cough. The disappearance of adventitious sounds with coughing probably indicates a benign condition.

Monitoring the length of inspiration versus expiration can be helpful. Normal vesicular breathing produces a long inspiration and shorter expiration. Bronchial breathing has a prolonged expiration indicative of early obstructive changes.

The optometrist should be reminded that beta-blockers used for the topical treatment of glaucoma can exacerbate asthma. Some patients may be unaware that they have asthma. It is therefore recommended that the optometrist contact the patient's physician to determine whether a pulmonary problem has been diagnosed before prescribing a beta-blocker.

EXAMINATION OF THE HEART

The most frequent cardiac complaints include chest pain, coughing, syncope, fatigue, palpitations, high blood pressure, dyspnea while lying flat or asleep, peripheral edema (fluid in the legs), and a history of heart attack or abnormal electrocardiograms (see Chapter 9). Before the advent of echocardiography, the clinical examination of the heart was the most elegant and most challenging in internal medicine. It was incumbent on the clinician to determine by clinical means whether a patient had a narrowing of the aortic valve, known as aortic stenosis, or a leaking valve causing aortic insufficiency or aortic regurgitation.

The clinician can hear systolic ejection sounds suggestive of an atrial septal defect, which is a hole in the superior aspect of the heart. The clinician might hear a click and a late systolic murmur associated with the most common valve abnormality, known as mitral valve prolapse.

The heart is examined in the context of its sounds, their radiation into the axilla or the neck, and the effect they have on the carotid pulse. Palpation is used to detect a displaced primary impulse, suggesting a change in the heart's size. Palpation can also detect abnormal movement of the blood through the heart, known as a thrill. The heart is percussed to determine whether it is enlarged.

Auscultation is carefully performed by listening for murmurs indicative of heart valve dysfunction. These murmurs are described in terms of their intensity, duration, location, and transmission. Many murmurs, if not most, are physiologic or functional. A murmur is a sound indicative of a relative increase in blood flow through the valve opening, and it suggests either a narrowing, a leak, or simply a normal variant. Other heart sounds that indicate malfunction, such as S_4 gallops, precede the first heart sound and are indicative of a noncompliant ventricle. An S_3 gallop follows the second heart sound and indicates a dilated or poorly functioning heart muscle.

The echocardiogram uses sound waves to measure the heart sound, as well as the function of the valve. It establishes whether a disease is present.

It is important for the optometrist to realize that beta-blockers may exacerbate bradycardia and other significant heart conditions. Before the optometrist treats glaucoma with topical beta-blockers, the patient's family physician should be consulted to verify that the drug will not exacerbate an underlying heart condition. Some heart conditions are treated with beta-blockers, and the patient may already be on such oral medications. Topical application of an additional beta-blocker may cause overdosage. To reduce the chance of systemic absorption of a topical beta-blocker, the patient must be taught the technique of punctal occlusion when an eye drop is applied.

EXAMINATION OF THE BREAST

Patients may have breast complaints, including lumps, discharge from the nipple, pain and tenderness, and abnormal findings from a self-examination. Breasts in both men and women should be examined in the routine medical examination. In men, palpation is used to detect the abnormal accumulation of breast tissue, known as gynecomastia, or the rare case of male breast cancer.

Examination of the female breasts involves visual inspection, followed by palpation. The skin of the breast is inspected for changes, lumps, retractions, and asymmetries. Palpation can determine whether dominant masses are present. Radiographs of the breasts (mammograms) or ultrasound, or both, are recommended to supplement the physical examination.

The breasts should be examined regularly, and a good physical examination should include education about the importance of monthly self-examination by the patient. Breast examination is not part of the routine optometric examination, and any patient with a breast complaint should be referred to a family physician or surgeon. A patient with a history of breast carcinoma requires a dilated fundus examination to rule out metastasis to the retina.

EXAMINATION OF THE ABDOMEN

Abdominal complaints include pain, nausea, vomiting, rectal bleeding, jaundice, and pruritus. The clinician should begin examination of the abdomen by inspecting for the obvious signs of obesity or muscular laxity. Scars, engorged veins, abdominal contours, and visible masses should be noted. The abdomen is then percussed to detect any enlargement of the liver or spleen, and any dullness suggestive of an underlying mass. The abdomen is then palpated, feeling for the liver's edge on the right side of the body and the

spleen's edge on the left. Sometimes abdominal palpation requires that the patient be placed in a left lateral position to ascertain enlargement. The examiner should palpate the midabdomen carefully, particularly in older patients, looking for signs of dilatation of the aorta, known as an aortic aneurysm.

The abdomen is then auscultated for bruits, which can indicate narrowing of the renal artery or the presence of atherosclerosis in the abdominal aorta. Auscultation is particularly important in the assessment of patients with unusual blood pressure elevations, because such elevations can be the result of narrowing, or stenosis, of the renal artery.

When abdominal distension is present, the clinician needs to look for the signs of ascites, which is fluid in the abdomen. Ascites can occur as a result of a generalized accumulation of fluid secondary to heart failure, liver failure, or tumors. Because fluid produces a change in the percussion sound, one clinical sign of ascites is a change in the distribution of dullness. The examiner can induce shifting of the dullness by placing a hand in the middle and tapping the side of the abdomen while turning the patient. In this way a fluid wave can be produced.

In addition to these physical signs, the clinician can use an ultrasound examination to confirm a clinical suspicion of ascites. The patient who is seen by the optometrist with symptoms of nausea, vomiting, and intestinal cramps, along with the ocular signs of uveitis, must be evaluated for inflammatory bowel disease (see Chapter 11).

EXAMINATION OF THE GENITOURINARY TRACT AND PELVIS

Typical pelvic complaints include pain, dysuria (pain on urination), incontinence, hematuria (blood in the urine), discharge, lesions, impotence, or dyspareunia (painful intercourse), infertility, and dysmenorrhea (painful menstruation).

A pelvic examination of the female patient begins with an inspection of the external structures for signs of abnormalities. The pelvic examination involves all of the physical examination skills and also a scraping of cells from the cervix, known as a Pap smear. Abnormal cervical cells may be the first sign of an underlying cervical or uterine malignancy. Next, a speculum is inserted into the vaginal canal to visualize the vaginal wall and cervix. The speculum is kept in place while a sample of the cervical and uterine cells are obtained for the Pap smear. The speculum is then removed.

Palpation is used to evaluate the size of the uterus, uterine irregularities, enlargement of the ovaries, or abnormal masses in the area surrounding the uterus. The clinician performs uterine palpation by inserting one finger into the vaginal canal while another finger deeply palpates the surface of the abdomen. A rectovaginal examination takes place to ascertain whether a fullness that is felt in the patient's side is caused by the bowel or to the pelvic organs. A pelvic examination is critical for early detection of cervical, uterine, or ovarian cancer.

The male genitals are inspected for changes in size of the external genitalia, particularly the testicles, and for lesions on the scrotum or penis. Palpation of the testicles is essential for determining symmetry, changes in abnormal lumps or bumps, and the presence of hardness. Testicular tumors are common tumors occurring in men younger than 30 years. Although female breast examination and screening have been given considerable media attention, the need to instruct men in routine genital self-examination is often overlooked.

Another common abnormality of the male genitalia is the varicocele, which is an abnormal dilatation of the vein of the spermatic cord. Varicoceles are usually asymptomatic, but they are sometimes implicated in cases of subfertility. Enlargements of the epididymis, known as spermatoceles, also may be noted and may require corroboration by a urologic specialist.

Coughing or straining is necessary to elicit hernias, which result from breaks or discontinuities in the abdominal wall, allowing herniation of bowel. This condition requires surgical repair.

EXAMINATION OF THE RECTUM

Constipation, diarrhea, and abdominal pain are complaints that necessitate a detailed rectal exam. In male patients, the rectal examination includes observation and palpation to determine the size and consistency of the prostate and to detect any signs of prostate cancer, early polyps, or tumors of the rectal area.

Examination of the rectum is improved by the use of an endoscope. A small anoscope is used to look for rectal abnormalities. Rigid sigmoidoscopes allow examination of 25 cm of the bowel. A flexible sigmoidoscope may extend to 60 cm.

The detail with which one approaches the examination depends on the age of the patient. Significant risk factors for colon cancer include the age of the patient and a family history of colon cancer (see Chapter 11).

EXAMINATION OF THE MUSCULOSKELETAL SYSTEM

Musculoskeletal complaints include paresis (weakness) or paralysis, muscle stiffness, joint pain, limited movement, and a history of gout, arthritis, or deformity. The clinician must perform the orthopedic examination in a disciplined fashion, looking at every joint and assessing the integrity of the joint for both

disease and function. Inspect for signs of inflammation, swelling, warmth, and redness, and examine each joint through its full range of motion. Whether it be the shoulder, the elbow, the knee, or the hip, each joint has a specific range of functional capabilities. Restrictions in function and elicitation of pain are important findings to record. They may be indicative of disease intrinsic to the joint, such as degenerative change or rheumatoid arthritis, or extrinsic to the joint, involving the tendons, muscles, or ligaments that surround it. The term arthritis is often used to describe musculoskeletal pain, but that diagnosis is appropriate only when inflammation of a joint is involved (see Chapter 13).

The clinician begins by examining the small joints of the hands and feet and then moves to the shoulders, elbows, wrists, hips, knees, and ankles. Next, the neck, midback, and lower back are examined. The neck has a prescribed range of motion, which includes flexion forward, extension backward, lateral rotation to the right and left, and flexion to each side. The measurement of each movement should be recorded in degrees, and any limitation, pain, or spasm should be noted.

The midback is inspected for lateral curvature, known as scoliosis, palpated for pain, and guided through a routine set of movements that indicate whether function is normal.

The same examination is performed on the lower back. Lower back evaluation is complex because the most common back afflictions involve irritation to the nerves that emanate from the spine and continue down the leg. For example, patients with knee pain may have an intrinsic disease of the knee, such as arthritis, bursitis, tendinitis, or torn cartilage. Alternatively, the pain may reflect irritation of the nerves that supply the knee from the level of the back.

The spinal examination also involves palpation of the sacroiliac joint and the sciatic notch to rule out irritation of the sciatic nerve at the level of the back. Even the examination of the legs is directed at determining dysfunction in the back. This examination includes maneuvers such as straight-leg raising, reflex examination, and determination of strength and sensation in the independently innervated areas of the foot.

The dorsal web of the foot is supplied by the nerves of the L5-S1 spinal disc and the medial aspect of the foot by those of the L4-L5 disc. Examination of these is more appropriate to the neurologic examination, but they are essential in examination of the back as well.

The optometrist must rule out significant collagen-vascular disease in all cases of anterior uveitis. Ankylosing spondylitis is typically found in a male uveitis patient, aged 20 to 40 years, with chronic lower back pain. A male patient in the same age group with arthritic joint pain and dysuria may have Reiter's syndrome. Young children who present with uveitis, particularly in a white, quiet eye, and who have posterior synechiae, cataract, and corneal edema or keratopathy, should be referred to a pediatric rheumatologist to rule out juvenile rheumatoid arthritis (see Chapters 13 and 21).

EXAMINATION OF THE LOWER EXTREMITIES

After the neurologic examination (see Chapter 2), the lower extremities are examined. The feet and legs are inspected for changes in color. A lack of hair growth may be indicative of poor arterial supply.

The pulses in the legs are assessed, starting with the femoral pulse in the groin, the popliteal pulse behind the knees, the posterior tibial pulse behind the ankle, and the dorsalis pedis pulse on the dorsum of the foot (approximately between the first and second toes).

Evaluation of arterial insufficiency in the legs is extremely important. To test the feet for swelling, place pressure on the skin and note whether a residual indentation remains, indicating peripheral edema. Palpate the calf for any abnormalities that might suggest deep vein thrombophlebitis.

In diabetics the skin of the feet should be inspected with special care, looking particularly between the toes for signs of cracking or fungal infection. The skin is also assessed for lesions, especially for evidence of dryness.

THE PHILOSOPHY OF THE PHYSICAL EXAMINATION

There are three categories of physical examination: the general physical, the focused examination, and the evaluation of a specific problem. The general physical provides an overall assessment of the patient. In the focused examination, a particular area of the body is inspected in great detail, and the entire examination is directed at that organ system or the related areas that might produce the patient's chief symptom. This is true, for example, in the assessment of the common problem of back pain. In that case, the back is inspected in greater detail, and a careful neurologic examination is made of the lower extremity to determine possible nerve dysfunction emanating from the back. The third category of physical examination focuses on the evaluation of a specific medical problem, such as headache (see Chapter 18).

SUMMARY

Medical technology has overshadowed the physical examination for many physicians. The care and detail once given to the cardiac examination are sometimes

dismissed, and the patient is simply referred for an expensive echocardiogram. The painstaking detail of a neurologic assessment is replaced by a magnetic resonance scan. The importance of palpating the prostate to detect early prostatic carcinoma has at times been supplanted by a screening blood test known as a prostate-specific antigen.

The physical examination suggests whether or not medical technology should be applied. The careful physical examination is the essence of the doctor's contribution to the patient's medical care and the basis for subsequent treatment.

It is hoped that this chapter provides a useful introduction and guide, a basis for continued learning, and a new attitude of respect for and interest in the elegance and significance of the physical examination.

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CHAPTER 3

The Neurologic Examination

CHAPTER OUTLINE

The visual pathway from the retina to the occipital lobe is so lengthy that intracranial lesions are likely to affect some part of the functional visual system. The key to diagnosis of the location and nature of such a lesion is the determination of its effect on the visual system and on other neurologic structures. The site of the lesion can be inferred from neurologic deficits identified by the practitioner. The lesion's location is confirmed by radiography, computed tomography (CT scan), or magnetic resonance (MR) imaging (see Chapter 5). Finally, the nature of the lesion is tentatively deduced from the radiographic results along with the patient's history, symptoms, and clinical signs.

This chapter describes a basic neurologic evaluation for the optometrist. The chapter first describes the evaluation of the patient's mental status, reflexes, sensory and motor functions, and cerebellar functions. The remainder of the chapter is devoted to evaluation of the cranial nerves.

THE PRINCIPLES OF NEUROLOGIC DIAGNOSIS

Patients may be seen by the optometrist with no complaints at all or with ocular or neurologic symptoms. Neurologic symptoms are clues that help the practitioner establish the presence of a lesion; these symptoms must be differentiated from a psychogenic problem or malingering.

The eye examination may reveal the presence of a visual pathway disturbance as evidenced by a decrease in visual acuity, pupillary defects, visual field changes on perimetry testing, color vision distortions, or optic nerve head problems.

Whether or not a defect is discovered in the visual pathway, a neurologic screening should be performed on every patient. If no ocular or neurologic deficits are discovered, the optometrist must determine the cause of any symptoms. If no symptoms or signs are present,

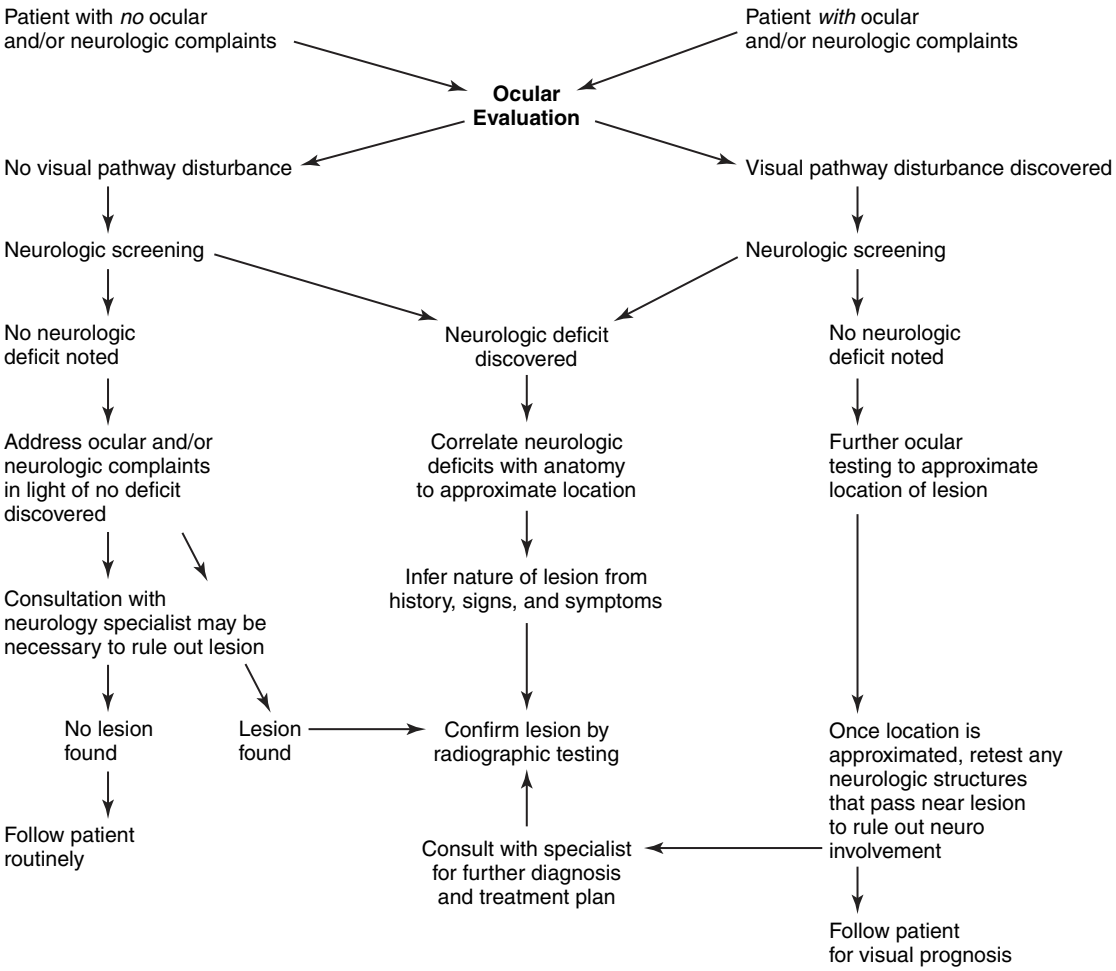


FIGURE 3-1 ■ Flow chart for the neurologic evaluation of the eye care patient.

the clinician should perform a routine examination. (Figure 3-1 is a flow chart for the neurologic evaluation of the eye care patient.)

Symptoms Without Clinical Signs

If no clinical signs are present in a symptomatic patient (Box 3-1), the clinician must rule out the presence of disease. This goal is accomplished by consultation with the family physician, neurologist, ophthalmologist, neuro-eye specialist, internist, or endocrinologist. For example, if a patient complains of headache and the ocular examination and neurology screening reveal no significant findings, one must decide whether to refer the patient for further evaluation or to monitor the patient oneself.

Radiographic studies and laboratory work may be necessary to establish a diagnosis. Psychogenic symptoms and malingering can be ruled out in this way.

BOX 3-1
SIGNIFICANT NEUROLOGIC SYMPTOMS

- Headache
- Confusion
- Unsteadiness
- Visual problems
- Speech problems
- Tremors
- Numbness
- Weakness

Visual Defects With No Obvious Neurologic Problems

If a visual pathway deficit is discovered but no neurologic problem is found, further neurologic testing is warranted to rule out the effects of a lesion on neurologic structures passing near the suspected site.

First, the location of the lesion is determined by its effect on the patient's visual field. With an intimate understanding of neuroanatomy, the optometrist can identify nearby neurologic structures and infer what neurologic deficits would occur if these nearby nerves

were damaged. Finally, the optometrist should perform the neurologic evaluation, paying particular attention to any deficits that would occur given the lesion's suspected location. The examiner should be careful to elicit only findings that are truly present.

Ocular and Neurologic Defects

A patient may have both ocular and neurologic defects. Whether the patient is symptomatic or asymptomatic, the examiner must correlate these findings with the relevant neuroanatomy to localize the lesion. The nature of the lesion may be tentatively inferred at this point on the basis of the patient's history, symptoms, and signs, and the approximate location of the lesion.

The differential diagnosis can be narrowed down by radiographic findings. Conventional radiography, CT scan, MR imaging, and color Doppler ultrasonography all help in determining the diagnosis (see Chapter 5).

In most cases the clinician will want to consult with a specialist, who will oversee the advanced diagnostic and treatment options available to the patient. Referral to a neurology specialist helps in pinpointing a more generalized problem. Treatment is determined by the cause of the lesion. Surgery or other forms of treatment may be recommended by vascular specialists or neurosurgeons. Eventually, low vision adaptations may be necessary.

THE NEUROLOGIC SCREENING

For practical purposes, the neurologic examination is divided into six areas that affect optometric practice: evaluation of the patient's mental status, motor function, sensory function, cerebellar functions, reflexes, and cranial nerve functions (Box 3-2).

BOX 3-2
THE NEUROLOGIC SCREENING

Mental status
Motor function
Sensory function
Cerebellar function
Reflex function
Cranial nerve function

TABLE 3-1 LOCALIZING VALUE OF MENTAL STATUS EVALUATION

MEDICAL CONDITION	DESCRIPTION OF PROBLEM	NEUROLOGIC SCREENING AFFECTED
Coma	Decreased level of consciousness	Nonlocalizing
Disorientation	Lack of orientation to time and place	Temporal lobe
Amnesia	Memory loss	Temporal lobe
Aphasia	Speech problem	Frontal, temporoparietal lobe
Inappropriate affect	Inappropriate emotional display	Bilateral cerebral damage
Agnosia	Inability to recognize objects	Nondominant parietal lobe
Apraxia	Inability to follow orders	Frontal lobe

BOX 3-3
EVALUATION OF MENTAL STATUS

Consciousness
Orientation
Memory
Speech
Appropriate affect
Object recognition
Praxis

Evaluation of Mental Status

Table 3-1 and Box 3-3 discuss the evaluation of mental status.

While talking with the patient, the optometrist should judge from his or her responses whether the patient seems alert and aware. Does the patient seem confused? Is he or she acting in a rational manner? Is the patient oriented to time and place? If the patient is disoriented, does he or she have short-term or long-term memory loss?

The examiner can test memory loss by presenting a set of three common words to the patient and asking him or her to repeat them minutes later. Memory loss may be caused by a temporal lobe lesion.

Is the patient speaking clearly and using vocabulary appropriately? A dysfunction in speech can help to localize a lesion. A patient who vocalizes meaningless words has dysphasia, which may indicate a brain lesion of the left hemisphere.

If a patient talks sensibly but has difficulty in producing sound, a disruption exists in the motor function that produces speech. This problem can occur anywhere along the pathway from the brain to the mouth.

Is the patient exhibiting inappropriate emotions, such as sudden laughter or crying? This type of emotional display may be the result of bilateral cerebral damage.

Can the patient recognize common objects? Inability to do so is called agnosia. If the patient cannot identify an object by touching it with eyes closed,

he or she may have a lesion in the nondominant parietal lobe.

Can the patient carry out simple instructions? Inability to do so is called dyspraxia and may be the result of a deep frontal lobe lesion.

Finally, can the patient copy a simple drawn figure? Inability to do so may be caused by a posterior parietal lobe lesion.

Evaluation of Motor Functions

Muscle weakness is a fairly nonlocalizing finding, because it can be caused by disturbances in the nerves, muscles, cerebrum, brainstem, spinal cord, or neuromuscular junction. To screen for muscle weakness, the examiner should ask the patient to flex and extend both arms and legs against resistance (Figure 3-2). Note any weakness of one limb when comparing the two.

Evaluation of Sensory Functions

Neurologic evaluation should include tests for the senses of touch, pain, and vibration. Loss of these senses may indicate a spinal cord lesion. The following tests are performed with the patient's eyes closed. To test for the sense of touch, stroke the patient's fingers with a tissue after asking him or her to tell you when he or she feels the stroke of the tissue (Figure 3-3). Repeat the test on the patient's toes.

To test for pain sensation, touch the patient on the fingers and hand with the point of a safety pin. Begin touching the fingers and hand, alternating the sharp tip with the blunt end, and determine whether the patient can discern the difference between sharp and dull sensations (Figures 3-4 and 3-5). Repeat this test on the patient's toes.

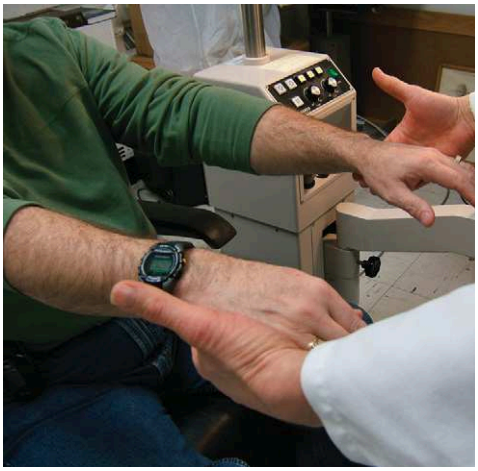


FIGURE 3-2 ■ Evaluation of motor function. To test the forearms for flexion and extension, the patient exerts force against the examiner, who holds the patient by the wrist. This procedure tests roots C5-C6 (flexion) and C6-C8 (extension).

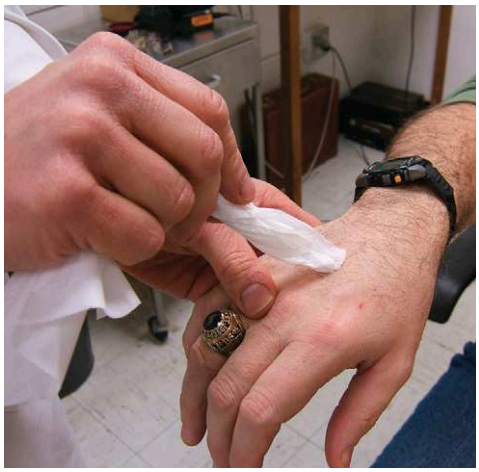


FIGURE 3-3 ■ Evaluation of tactile sense. The patient is asked to close his or her eyes. His or her fingers and toes are lightly touched with a tissue. A significant finding is a marked decrease in sensitivity.

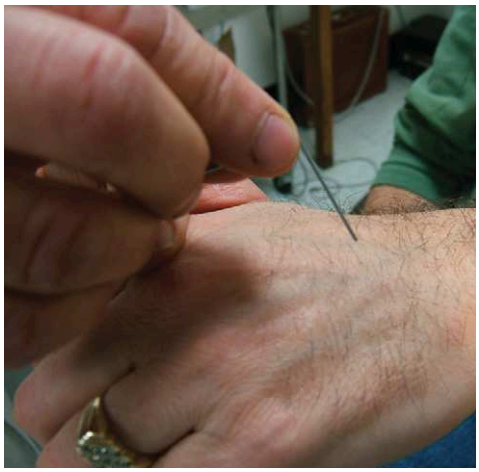


FIGURE 3-4 ■ Evaluation of pain sense. The patient is asked to close his or her eyes. With the sharp end of a safety pin the fingers and toes are lightly pricked.

Finally, test vibration sense using a 128-Hz tuning fork. Strike the tuning fork with your hand and place it over the base of the nail bed on the patient's index finger. Place your index finger under the patient's fingertip so you can feel the vibration also (Figure 3-6). Ask the patient to report when he or she no longer feels the vibration.

Evaluation of Cerebellar Functions

To test for cerebellar disorders, perform a "finger-to-nose" test. Hold your finger at arm's length from the patient. Ask the patient to touch his or her nose with his index finger and then touch your index finger. Repeat this several times with the patient's eyes open and then closed (Figure 3-7). A patient with a disorder

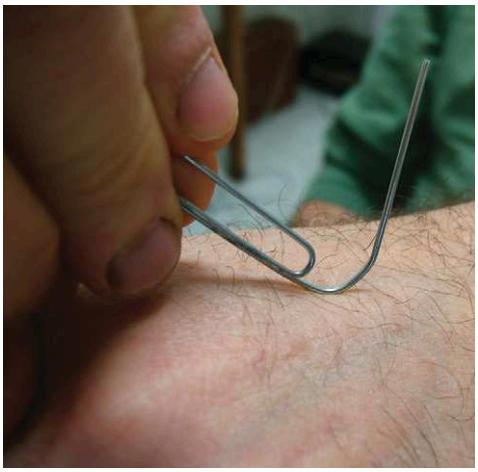


FIGURE 3-5 ■ Evaluation of pain sense. The procedure described in Figure 3-4 is repeated with the dull end of the pin. The examiner alternates the sharp and dull ends of the pin, and the patient is asked to compare sharp and dull sensation while the examiner moves proximally.

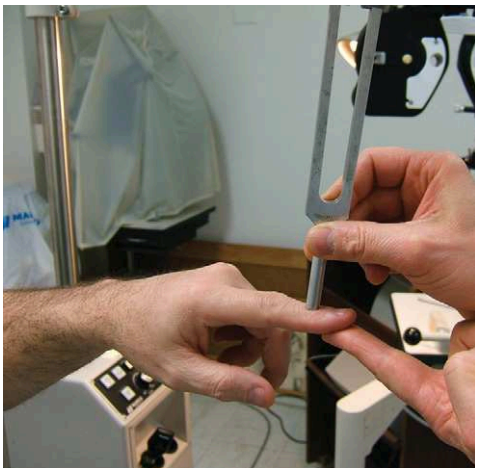
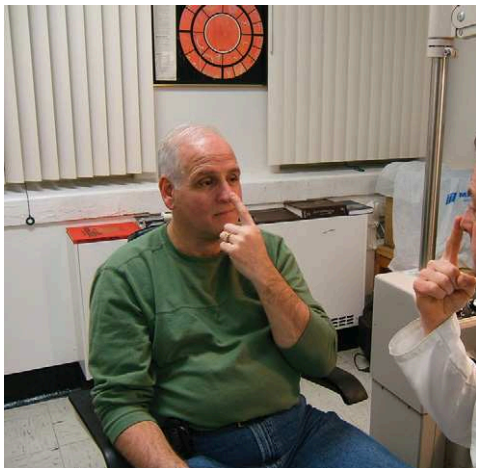


FIGURE 3-6 ■ Evaluation of vibration sense. A 128-Hz tuning fork is tapped to produce a vibration. The base of the fork is placed on the base of the patient's fingernail. The patient closes his or her eyes and reports when he or she can no longer feel the vibration. A significant finding is a reduced vibration sense.

of the cerebellum tends to overshoot the target. This response is called past pointing.

Another convenient test for cerebellar function is the Romberg test. Have the patient stand in front of you with heels and toes together. Then, ask the patient to close his or her eyes and attempt to maintain balance. Be prepared to catch the patient if he or she falls off balance. This test assesses the posterior columns.

You may also ask the patient to raise his or her arms palms up while balancing with eyes shut (Figure 3-8). Patients with a hemiparesis will drop one arm and flex the fingers. This condition is called pronator drift.



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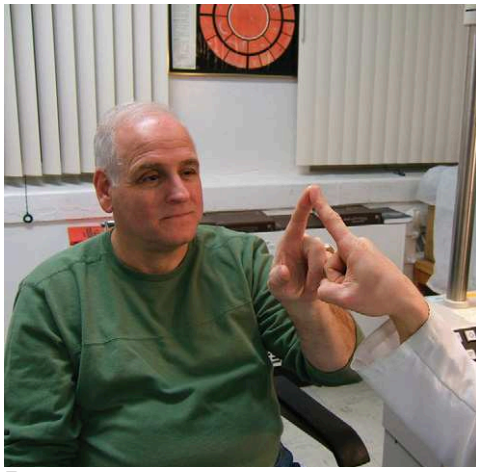

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FIGURE 3-7 ■ **A** and **B,** Evaluation of cerebellar function ("finger-to-nose" test). The examiner holds his or her finger outstretched at arm's length from the patient. With eyes open, the patient first touches his or her nose and then touches the examiner's finger. This sequence is repeated several times. Next, it is repeated with the patient's eyes shut. Cerebellar disease causes overshooting of the target and digital tremor.

The most important cerebellar function test is examination of gait (Figure 3-9). First, observe the patient as he or she walks away from you. Next, have the patient walk toward you on his or her toes. Finally, have the patient walk away from you, putting heel to toe. Loss of this ability can occur in cerebellar dysfunction caused by such diseases as syphilis.

Watch for normal posture and proper arm movement. Cerebellar ataxia is heightened by gait testing. Lower extremity muscle weakness may also be evaluated in this way.

Evaluation of Reflexes

The neurology tests should include an evaluation of deep tendon reflexes. A loss of these reflexes may occur in some cerebellar disorders. Of the many reflex

FIGURE 3-8 ■ Variation of the Romberg test for pronator drift.

FIGURE 3-9 ■ Examination of gait.

tests to choose from, the patellar tendon reflex test is most important.

Have the patient sit on the edge of a table or chair and dangle his or her feet. Place your hand on the quadriceps muscle of one leg and strike the patellar tendon with a reflex hammer. You should feel the quadriceps contract and see the knee extend (Figure 3-10).

Loss of deep tendon reflexes occurs in 50% to 90% of patients with Adie's syndrome. Bilateral Adie's tonic pupils, which are typically mid-dilated, may be confused with bilateral Argyll Robertson tonic pupils caused by syphilis, although these are typically constricted. Deep tendon knee reflexes help the examiner to confirm the presence of Adie's pupil, because this reflex is not lost in patients with Argyll Robertson pupil.

CRANIAL NERVE TESTING

The cranial nerves control the five senses, allowing the patient to interact with the environment, to feel it, move through it, experience it, and alter it. These twelve pairs of nerves, which extend from the brain to vital organs throughout the body, are necessary for the patient's everyday activities.

The cranial nerves may be affected by a wide range of conditions, including trauma, infection, demyelination from multiple sclerosis, cerebrovascular ischemia from stroke, intracranial inflammation from meningitis, and development of space-occupying lesions (such as tumors or aneurysms). The cranial nerves receive sensory (afferent) input from internal organs and from the skin, as well as special sensory input from the eyes, ears, and nose. The motor (efferent) innervation is supplied through the cranial nerves to voluntary and involuntary muscles throughout the body.

The functioning of each cranial nerve should be tested and evaluated. All of the following tests can be performed in the optometrist's office (Table 3-2).

First Cranial Nerve—Olfactory Nerve

The olfactory nerve is a special afferent cranial nerve composed of sensory fibers only. The sole function of this nerve is olfaction, the ability to discern smells. To test the olfactory nerve, the examiner should ask the patient to shut his or her eyes and occlude one nostril. The patient's open nostril is presented with a variety of vials, each containing a concentrated extract such as coffee, vanilla, or peppermint. The patient is asked to sniff

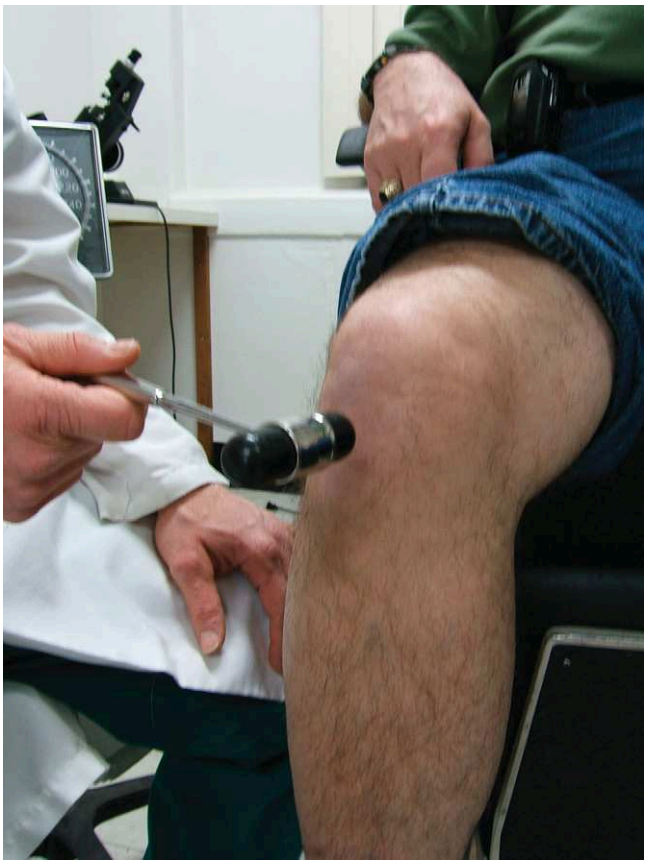

FIGURE 3-10 ■ Evaluation of deep tendon reflexes. The patellar tendon reflex is tested by positioning the patient on the edge of the examination chair or table so that his or her legs dangle freely with no obstruction. The examiner lightly places one hand on the quadriceps muscle. The patellar tendon is struck firmly by the base of the hammer. Extension of the knee should occur, and contraction of the quadriceps should be felt. This procedure tests the nerves at roots L2 to L4.

and identify each smell (Figure 3-11). The loss of olfactory ability is called anosmia and can be caused by viral infection, trauma to the skull, or frontal lobe masses or seizures. Olfactory nerve testing is rarely performed, because it is an unreliable test of cranial disease.

Nasal polyps are the most common cause of anosmia. The loss of smell on one side is more ominous than bilateral anosmia, because it indicates a possible lesion affecting the ipsilateral olfactory nerve or tract.

Second Cranial Nerve—Optic Nerve

Like the olfactory nerve, the optic nerve contains only special sensory afferent fibers. The optic nerve functions to convey visual information from the retina to the occipital lobe through the visual pathway. The optic nerve is tested in the office by visual acuity measurement, color testing, pupil testing, visual fields testing, and optic nerve head evaluation with an ophthalmoscope or stereo biomicroscopy.

Visual fields testing has great localizing value when an intracranial lesion affects the visual pathway. Prechiasmal lesions usually cause monocular field defects. Chiasmal lesions produce heteronymous hemianopsia, and postchiasmal lesions produce homonymous hemianopsia. The more posterior the lesion, the more congruous (alike) the two fields appear.

Third Cranial Nerve—Oculomotor Nerve

The oculomotor nerve contains only motor fibers, of which there are two types. Somatic efferent fibers innervate the medial rectus, inferior rectus, superior rectus, levator palpebral superioris, and the inferior oblique muscles of the eye. Visceral efferent motor fibers innervate the constrictor pupillae and ciliary muscles with parasympathetic fibers from the ciliary ganglion.

Because the third nerve innervates four of the six extraocular muscles, testing is performed by having the patient's eyes follow a near target while the examiner draws out a physiologic "H" pattern, causing adduction (medial rectus), depression while abducting (inferior rectus), and elevation (superior rectus and inferior oblique). Pupillary constriction is tested by the light reflex, and accommodation can be tested on a near target. Loss of third-nerve function may cause diplopia and an eye that is "down-and-out" with ptosis and mydriasis.

Fourth Cranial Nerve—Trochlear Nerve

The trochlear nerve supplies only somatic efferent motor fibers to the superior oblique muscle of the eye. The superior oblique is tested, as previously described, by having the patient's eyes follow a near target while the examiner traces an "H" pattern. The trochlear nerve causes superior oblique contraction, which rotates the eye inward, downward, and outward. To best isolate this nerve, the examiner should have the patient adduct and look down toward the nose.

The trochlear nerve is the only cranial nerve to exit from the dorsal aspect of the brain, and it has the longest intracranial course of any cranial nerves. Lesions that affect the fourth nerve include injury, inflammatory disease, compression from an aneurysm of the posterior cerebral and superior cerebellar arteries, and cavernous sinus entities. A lesion that affects the trochlear nerve causes diplopia and torticollis (twisted neck).

Fifth Cranial Nerve—Trigeminal Nerve

The trigeminal nerve supplies both sensory and motor fibers to the face and periorbital area. The afferent sensory fibers supply sensation to the face, scalp, tongue, teeth, conjunctiva, tympanic membrane, and mucous

TABLE 3-2 THE CRANIAL NERVES

CRANIAL NERVE	NO.	INNERVATION	PRIMARY FUNCTION	TEST
Olfactory	1	Sensory	Smell	Identify odors
Optic	2	Sensory	Vision	Visual acuity, visual fields, color, nerve head
Oculomotor	3	Motor	Upper lid elevation Extraocular eye movement Pupil constriction Accommodation	Physiologic "H" and near point response
Trochlear	4	Motor	Superior oblique muscle	Physiologic "H"
Trigeminal	5	Motor	Muscles of mastication	Corneal reflex
		Sensory	Scalp, conjunctiva, teeth	Clench jaw/palpate Light touch comparison
Abducens	6	Motor	Lateral rectus muscle	Abduction/physiologic "H"
Facial	7	Motor	Muscles of facial expression	Smile, puff cheeks, wrinkle forehead, pry open closed lids
Vestibulocochlear	8	Sensory	Hearing Balance	Rinne test Weber test
Glossopharyngeal	9	Motor	Tongue and pharynx	Gag reflex
		Sensory	Taste-posterior one third of tongue	
Vagus	10	Motor	Pharynx, tongue, larynx, thoracic and abdominal viscera	Gag reflex
		Sensory	Larynx, trachea, esophagus	
Accessory	11	Motor	Sternomastoid and trapezius muscles	Shrug, head turn against resistance
Hypoglossal	12	Motor	Muscles of tongue	Tongue deviation

FIGURE 3-11 Testing the olfactory nerve. One nostril is occluded by the examiner. The patient is asked to sniff extracts of vanilla, coffee, and peppermint, and attempts to identify each of them.

membranes of the paranasal sinuses. Motor efferent fibers function to innervate several facial muscles, including the muscles of mastication.

Three tests are used to evaluate the trigeminal nerve: the corneal reflex test, the sensory division test, and the motor division test. The examiner evaluates the corneal reflex by gently touching the temporal side of the cornea with a thin sterile braid of cotton while the patient looks down and toward his nose. Normally, the patient immediately shuts his eyes. This procedure tests both the sensory fifth nerve and the motor portion of the seventh, or facial, nerve, which is responsible for lid closure (Figure 3-12, *A*).

To test the sensory division of the fifth nerve, the examiner should ask the patient to close his or her eyes, and then lightly touch one side of the patient's forehead with a tissue. Next, the examiner should touch the other side and ask the patient to compare sensations. A reduced sensation of touch on one side may indicate a hemiparesthesia. The test is repeated on the cheeks to test the second division of the trigeminal and on the chin to test the third division (Figure 3-12, *B*).

To test the motor component of the trigeminal nerve, the examiner should ask the patient to clench his or her teeth to produce a prominence of the masseter muscle. The examiner should palpate both masseters and compare the muscle tone of both (Figure 3-12, *C*).

One of the most common causes of sensory loss of the fifth nerve is fracture of a facial bone, especially a blow-out fracture of the orbital floor. This trauma may cause ipsilateral reduction or loss of feeling on the cheek. Vascular damage, tumors of the pons, and trauma may cause damage to the motor neuron or its axons.

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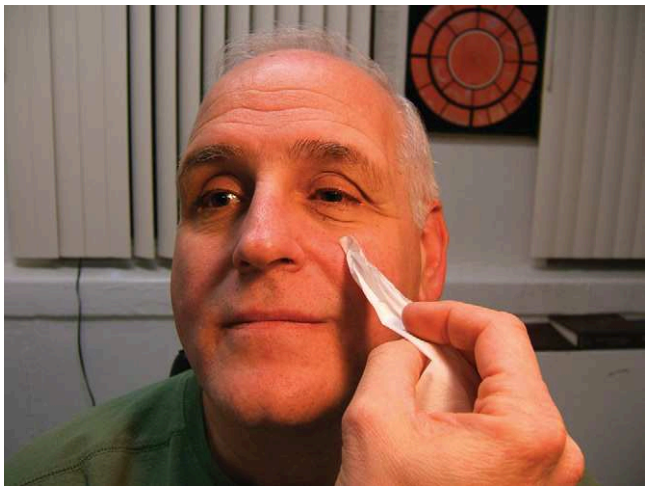

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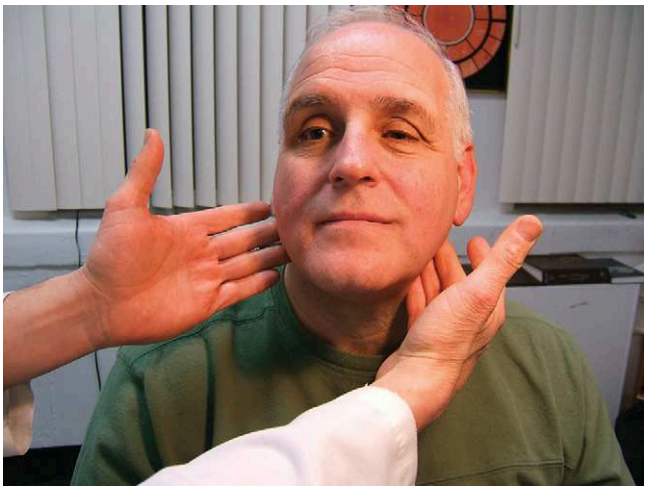

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FIGURE 3-12 ■ Testing the trigeminal nerve. **A,** The corneal reflex. The patient is asked to look downward and inward while the examiner touches the temporal cornea with a small bit of cotton. Immediate closure of both eyelids should occur. **B,** The sensory distribution of the trigeminal nerve is tested by asking the patient to compare the sensation of light touch on both sides of the forehead, cheek, and chin. **C,** The motor component of the trigeminal nerve is tested by palpating the masseter muscles of a patient who is clenching his or her teeth and comparing the muscle tone of both sides.

A blow-out fracture can cause numbness to the gum behind the incisor. To test this, the examiner should push the wooden end of a sterile, cotton-tipped applicator gently into the patient's gum behind the incisor tooth of the uninvolved side. The procedure is repeated on the involved side, and the patient is asked to compare the sensations on both sides. A blow-out fracture of the orbital floor can cause a reduced sensation to this area of the gum on the ipsilateral side.

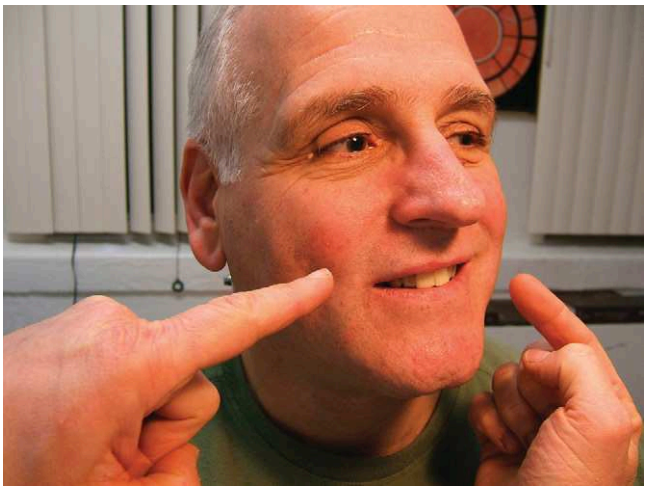
Sixth Cranial Nerve—Abducens Nerve

The abducens nerve supplies only somatic efferent motor fibers to the lateral rectus muscle of the eye. This muscle functions to abduct the eye.

To test the abducens nerve, have the patient's eyes follow a near target through the physiologic "H" pattern. An inability to abduct the eye indicates a possible abducens deficit. Patients with abduction deficit may complain of diplopia and may appear esotropic. Causes of abducens deficit include trauma, meningitis, cerebellar tumors, increased intracranial pressure, and cavernous sinus pathology, and aneurysms of the posterior cerebellar or basilar arteries or internal carotid arteries.

Seventh Cranial Nerve—Facial Nerve

The facial nerve supplies efferent motor innervation to the muscles of facial expression and lacrimal gland (and others), and sensory afferent fibers from the anterior two thirds of the tongue for taste. Testing of the facial nerve involves examination of the muscles it innervates. Four tests can easily evaluate the seventh nerve. First, the examiner should ask the patient to smile or bare his or her teeth without laughing, and look for any asymmetry of the cheeks that might indicate a hemiparesis of the nerve (Figure 3-13, *A*). Next, the clinician should push in on the patient's cheeks with the fingers while the patient attempts to puff out both cheeks. Then, the patient should attempt to wrinkle his or her forehead. A weakness on one side of the forehead causes a diminution in the wrinkling on the affected side (Figure 3-13, *B*). Finally, the patient should tightly shut his or her eyes while the examiner



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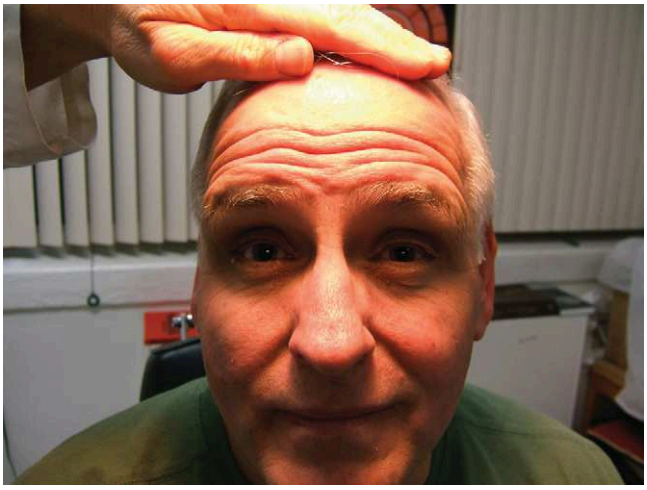

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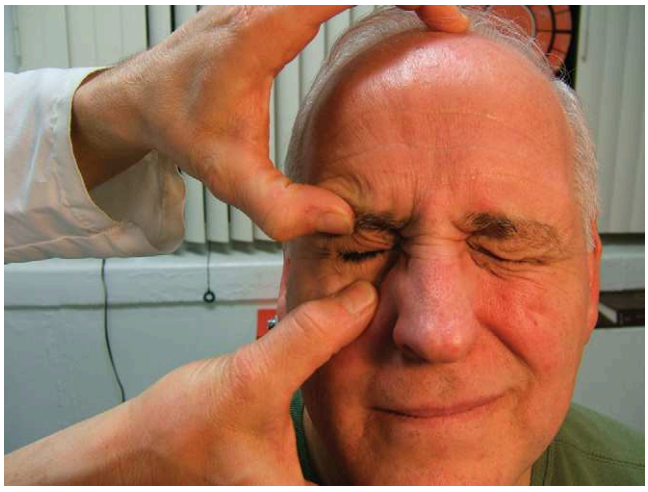

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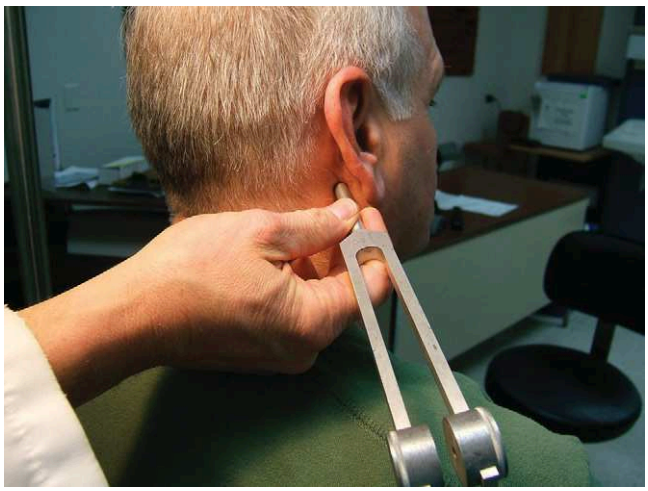
FIGURE 3-13 ■ Testing the facial nerve. **A,** The patient bares his or her teeth and the nasolabial folds on either side of the face are compared. **B,** The patient wrinkles his or her forehead and the wrinkling of the two sides is compared. **C,** The examiner attempts to pry open the patient's tightly shut eyelids.

attempts to pry the eyelids open. A weakness of the facial nerve allows for a relatively easy parting of the lids (Figure 3-13, *C*).

Bell's palsy is a common lower motor neuron lesion of the facial nucleus or its axon. All voluntary and reflex muscles ipsilateral to the lesion are affected. The result is facial asymmetry with drooping of the eyebrow, a smooth nasolabial fold, drooping of the corner of the mouth, and a reduced blink reflex on the affected side. All patients who have a new case of Bell's palsy should have a Lyme titer determination, because Lyme disease can produce hemifacial palsy (see Chapter 6).

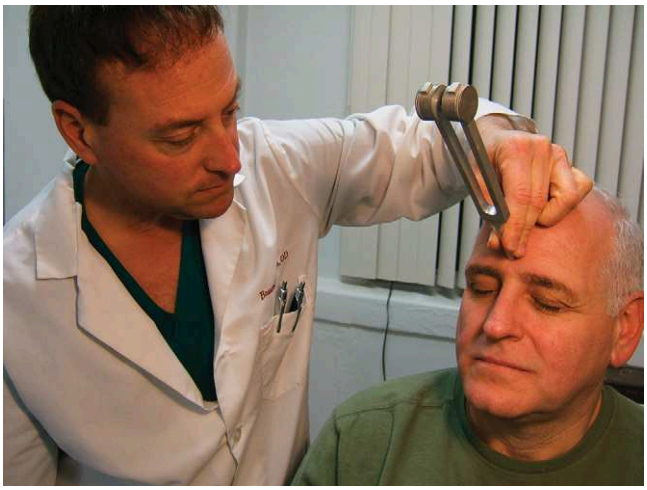
Eighth Cranial Nerve—Vestibulocochlear Nerve

The eighth cranial nerve is composed of two special sensory afferent fibers. One fiber controls vestibular function, or balance, and the other controls audition, or hearing. Evaluation of the eighth cranial nerve for audition is covered in Chapter 2. The Rinne and Weber's tests are easy to perform in the examination room and can help the examiner differentiate conductive deficits from neurosensory lesions (Figure 3-14) (see Chapter 2). No useful screening test currently exists to evaluate balance or vestibular function. Damage to the hearing apparatus or eighth cranial nerve can be caused by tumors, injury, or infection. Damage to the vestibular apparatus is most often caused by a tumor called an acoustic neuroma, which leads to nausea, deafness, dizziness, tinnitus, hearing loss, Bell's palsy, and loss of balance. These symptoms occur because the eighth and seventh nerves run together along part of their paths.



A

FIGURE 3-14 ■ Testing the vestibulocochlear nerve. **A,** The Rinne test for audition. A tuning fork is held against the mastoid process until the patient can no longer hear it. The still-vibrating fork is then brought to the ear.



B

FIGURE 3-14—cont'd ■ **B,** The Weber test for audition. A tuning fork is struck and placed in the center of the forehead, and the patient compares the loudness on both sides.

Ninth Cranial Nerve—Glossopharyngeal Nerve

The ninth cranial nerve supplies motor fibers to the parotid gland and the pharynx. It also supplies sensory fibers from the carotid body (to monitor oxygen tension in the blood) and from the posterior third of the tongue, mediating the taste sensation in the posterior tongue. Because the ninth cranial nerve innervates the pharynx, testing the gag reflex evaluates the integrity of the nerve. Light stroking of the wall of the pharynx should cause the patient to gag. A damaged nerve results in an absence of this reflex. The tenth and eleventh cranial nerve pathways are so close to those of the ninth that one rarely sees an isolated lesion of one of these nerves.

For an additional test of the integrity of the ninth and tenth nerves, the examiner should ask the patient to open his or her mouth and say "ahh." This action raises the soft palate high up in the back of the oral cavity. The uvula, a small, cone-shaped piece of tissue suspended from the back of the throat, should elevate without lateral deviation (Figure 3-15). Paralysis of the ninth nerve causes a pulling of the uvula to the unaffected side.

Tenth Cranial Nerve—Vagus Nerve

The tenth cranial nerve contains both sensory and motor components. The nerve receives sensory afferent fibers from the larynx, trachea, esophagus, pharynx, and abdominal viscera, and sends efferent motor fibers to the pharynx, tongue, larynx, and thoracic and abdominal viscera.

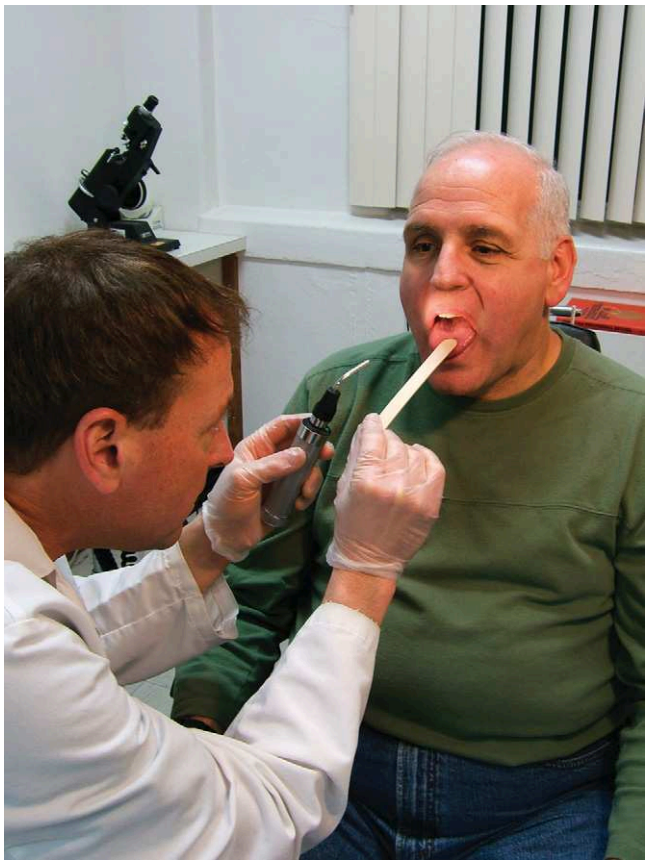


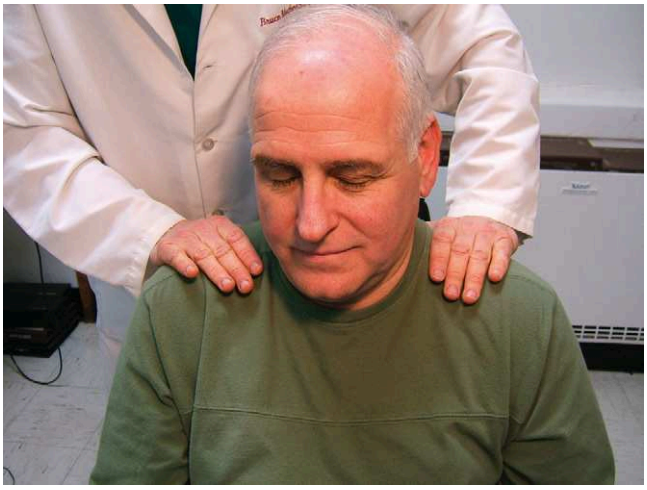
FIGURE 3-15 ■ Testing the glossopharyngeal nerve and vagus nerve. The patient sticks out his or her tongue and says "ahh." This action elevates the soft palate. The uvula should elevate without lateral deviation.

A unilateral lesion that affects the vagus nerve causes a loss of laryngeal function, producing hoarseness and difficulty in swallowing. To evaluate the vagus (and the ninth cranial nerve), the examiner should perform the "ahh" test described in the preceding section on the ninth cranial nerve (see Figure 3-15). Causes of unilateral vagus lesions include trauma from surgical procedures of the neck (such as carotid endarterectomy or thyroidectomy), aortic aneurysm, and metastatic carcinoma, in which enlarged paratracheal lymph nodes can compress the vagus nerve.

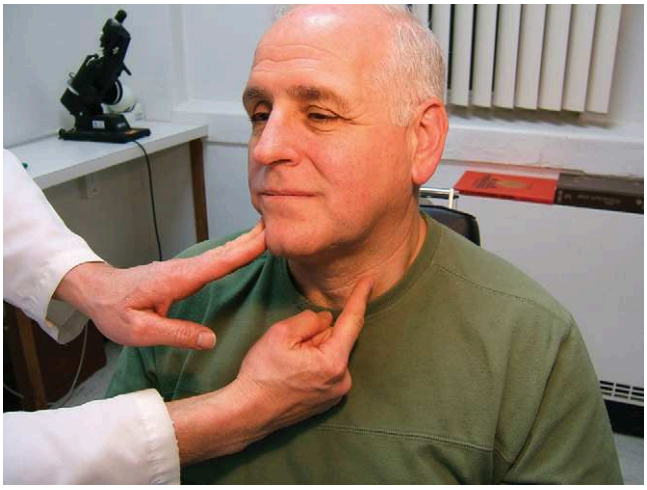
Eleventh Cranial Nerve—Accessory Nerve

The accessory nerve carries only efferent motor fibers to supply innervation to the sternomastoid and trapezius muscles. Damage to this nerve causes a drooping of the ipsilateral shoulder and loss of trapezius function on the affected side. The patient may have difficulty turning his or her head to the side that is opposite the lesion.

To test the eleventh nerve, place your hands on the patient's shoulders and press downward while the patient attempts to shrug the shoulders against your resistance (Figure 3-16, *A*). Another test involves having the patient attempt to turn his or her head against resistance. Place your hand on the left side of the patient's face and push against the patient's left cheek while he or she tries to turn his or her head to the left. Palpate the patient's right sternomastoid muscle and feel it tighten while the patient attempts to turn his or her head to the left. Repeat the process with the patient attempting to turn his head to the right against resistance (Figure 3-16, *B*). Damage to the eleventh cranial nerve can occur as a result of radical nerve surgery or trauma.



A



B

FIGURE 3-16 ■ Testing the accessory nerve. **A,** The examiner pushes down on the shoulders of the patient, who tries to shrug against the resistance. **B,** The patient turns his or her head against the examiner's hand while the sternomastoid muscle is palpated for tone. The patient then turns to the other side. The muscle tone on both sides is compared.

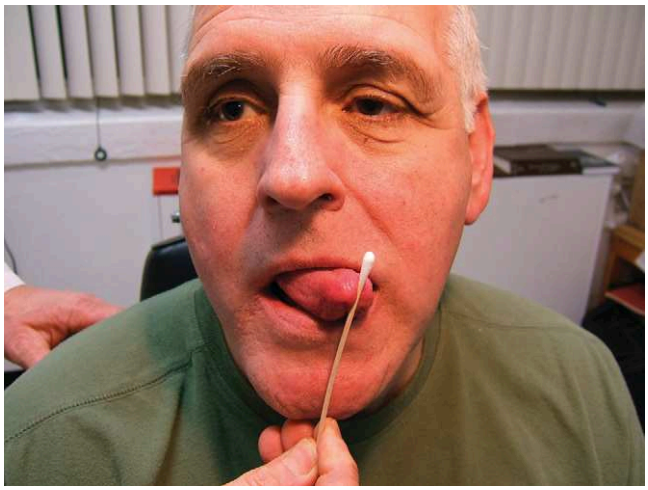


FIGURE 3-17 ■ Testing the hypoglossal nerve. The patient sticks out his or her tongue and moves it laterally against resistance from a cotton-tipped applicator.

Twelfth Cranial Nerve—Hypoglossal Nerve

The twelfth cranial nerve supplies efferent motor fibers to all intrinsic and extrinsic muscles of the tongue (except the palatoglossus). Damage to the nerve results in paralysis of the tongue on the affected side. Therefore, when the patient sticks out his or her tongue, it will deviate to the side of the lesion (Figure 3-17).

To test the hypoglossal nerve, the examiner should ask the patient to stick out his or her tongue and move it right and left against resistance offered by the examiner, who holds a cotton-tipped applicator to the lateral aspect of the tongue.

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CHAPTER 4

Laboratory Testing

CHAPTER OUTLINE

For the most part, eye disease can be diagnosed from a careful history, symptoms, clinical signs, and in-office procedures. The diagnosis of systemic disease with ocular manifestations, however, mandates the use of laboratory medicine. The use of laboratory testing can assist the optometrist in developing a differential diagnosis and may help in the detection or confirmation of a disorder. Once the diagnosis is established, laboratory testing may help the clinician in determining the prognosis of the disease and in monitoring the effectiveness of therapy. In this regard, laboratory testing impacts heavily on modern eye care. Routine blood testing and urinalysis are ordered for the preoperative medical evaluation of patients awaiting ocular surgery. The eye-care practitioner can use portable and relatively inexpensive instruments to monitor blood serum and urine glucose levels in a patient who has or who might have diabetes mellitus. Patients who are seen with hypertensive retinopathy, retinal arteriolar sclerotic changes, and retinal vascular plaques can have their serum cholesterol and triglyceride levels determined by in-office tabletop instruments. A battery of special hematology, chemistry, and immunology laboratory tests is used to evaluate systemic disorders underlying recurrent uveitis. The patient who has the early signs of Graves' thyroidopathy should have laboratory testing to evaluate endocrine function. Infections such as gonorrhea, toxoplasmosis, and cytomegalovirus retinopathy are detected by serology testing. For the most part, the optometrist can diagnose eye disease using a careful history, symptoms, clinical signs, and in-office procedures. The diagnosis of systemic disease with ocular manifestations, however, mandates the use of laboratory medicine.

POINT-OF-CARE TESTING

Point-of-care (POC) testing brings the laboratory to the optometry office so that a patient may be tested at the site of the examination. POC testing can be helpful in acute cases of sudden refractive shifts that are possibly caused by undiscovered diabetes mellitus.

Measurements of such a patient's serum glucose level, which are obtained quickly, allow the optometrist to identify a critical systemic crisis and intervene in a timely and appropriate manner. Portable instrumentation has become available in recent years that permit the analysis of blood and urine in the optometry office. Although most relevant for the identification of diabetes, these portable chemistry analyzers provide results for a number of tests, including cholesterol and triglyceride levels. The optometrist who wishes to participate in such POC technology should be aware of some significant factors influencing in-office lab testing, including cost, accuracy, training, safety, relevance, billing to the patient, and maintenance of equipment. The optometrist should check with his or her state optometry board to make sure that drawing blood in the office is legal. In some states, the drawing of blood without supervision of a pathologist or a medical doctor is considered practicing medicine without a license. In addition, the malpractice insurance carrier of the optometrist may feel that such POC procedures do not fall within the purview of optometry, and may not cover misdiagnosis or unexpected and unwanted incidents during blood or urine testing. In-office identification of the undiscovered diabetic is unlikely to be worth the time, effort and cost to the private practitioner. In cases of uveitis, in which a significant number of laboratory tests may be needed to find a systemic cause, POC has little if any relevance, and the local laboratory's facilities are mandatory.

The Clinical Laboratories Improvement Act of 1988 (CLIA-88) prohibits a laboratory from accepting human specimens for analysis unless it holds a certificate issued by the Secretary of the Department of Health and Human Services (HHS) for each category of testing that is to be performed. Because a laboratory is defined as "a facility for the examination of materials derived from the human body for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings," then in-office POC procedures may cause the private optometry office to be classified as a laboratory. In 1992, all laboratories, including in-office laboratories, were required to register with the federal government before performing any analysis used in patient care. In effect, CLIA-88 mandates that any laboratory that performs blood testing must be accredited by the federal government, pay a registration fee, document all laboratory procedures, submit to quality control and assurance monitoring and inspections, and pay fines if the office is found in violation of the law.

Devices used for at-home determination of blood glucose and total cholesterol and urinalysis, are considered under CLIA-88 to be "waived tests" and, as such, are exempt from quality assurance and proficiency testing. Laboratories that perform only waived tests, as in the case of an optometry office that uses home-testing devices (i.e., the Accumeter, Accucheck, ChemTrak), however, must still register with the federal government, pay a biennial fee, and comply with their state board of optometry requirements for in-office lab testing.

THE LOCAL LABORATORY

To gain familiarity with laboratory testing, the optometrist should meet with the laboratory manager of the local medical laboratory and tour the facilities. The practitioner should observe how the tests are actually performed. The laboratory will give instructions on how to order specific tests, what instructions the patient needs to follow (such as fasting before a procedure), what forms need to be filled out, where the patient is to report or where the sample needs to be sent, and the cost of the test. Be sure to get a laboratory user's guide from the laboratory. This guide lists all the tests available, as well as information concerning each test, how the sample is collected, patient preparation, interpretation of results, and methodology. This guide and the laboratory manager are invaluable sources of information when laboratory testing is indicated.

THE LABORATORY STRUCTURE

The medical laboratory is composed of several sections. These sections include anatomic pathology to examine tissue biopsy and acid-fast stains, the blood bank for transfusions, the chemistry section to analyze myriad blood compounds, hematology to study the cells and plasma of the blood, immunology to detect infections and inflammation, microbiology to identify infectious agents, nuclear medicine to scan tissues and organs using injected radiopharmaceuticals, and urinalysis. The individual laboratory tests ordered on a given patient fall under one of these sections.

BLOOD ANALYSIS

The chemicals, solids, and plasma of the blood may be analyzed by a wide variety of laboratory techniques. The study of the formed elements of the blood and the blood-forming tissues is known as hematology. The biochemical make-up of the blood, which can reflect the presence of systemic disease, is analyzed in chemistry. Immunology serum testing analyzes diseases characterized by antibody-antigen reactions. Blood cultures to detect, isolate, and identify potentially pathogenic organisms causing bacteremia are studied by microbiology. Nuclear medicine makes use of radionuclides in the diagnosis and management of disorders, and in some cases blood must be sampled and analyzed.

Blood Appropriation

Blood may be obtained from capillaries, vein, or bone marrow for laboratory analysis. The wearing of gloves is mandatory for all laboratory workers handling bodily fluids. If a danger exists of sample splashing, then staff should wear a gown and goggles.

Fingerstick (Finger Puncture)

Blood taken from a finger capillary is of a small volume and is used when a larger amount of venous blood is not needed or cannot be obtained. Fingerstick is the method of choice for in-office POC procedures. This method is most useful for single chemical tests, such as glucose or cholesterol levels, and has the advantage of being an easy technique for patients to learn when personal sampling is necessary. Fingerstick is inexpensive and does not require trained personnel or a specialized environment, and is relatively painless. This method may not be as accurate as venous blood sampling, however, and may not provide enough volume to perform a blood chemistry profile.

To perform skin puncture, an appropriate puncture site must be selected. In adults, this is usually the palmar surface of the last digit of the second, third, or fourth finger. The earlobe is a good alternate site. In infants, the lateral or medial plantar heel surface is most appropriate. The chosen puncture site can be warmed with a moist towel to increase blood flow through the capillaries. The site is then cleansed with 70% aqueous isopropanol solution and dried. The puncture is made with a sterile lancet in a deliberate motion perpendicular to the skin surface.

To sample the blood, the first drop of blood should be wiped away. The site should not be "milked" because this may introduce excessive tissue fluid into the sample. The sample is collected into a suitable container by capillary action. Alternatively, the sample may be placed directly on a reagent strip for an in-office single analysis test with use of a portable analyzer. Collection tubes should then be sealed and marked with the patient's demographics for shipment to the lab.

Venipuncture

Large samples of blood may be obtained from the superficial veins of the midarm, wrist, and back of the hand. These sample sizes are appropriate for blood chemistry profiles and special blood testing.

To obtain venous blood from the midarm, the patient must first be appropriately identified. If fasting is required, it must be confirmed that the patient did indeed fast. The patient is positioned properly, whether sitting or prone. The practitioner must wear gloves and a coat according to safety standards. The patient is instructed to make a fist and a suitable vein is identified; most often, one of the veins of the antecubital fossa is used. The area is cleansed with 70% isopropanol alcohol and then a tourniquet is applied several inches above the site of the needle insertion. The tourniquet should never be left on for longer than a minute. A needle is inserted into the vein and an evacuated container is connected to the needle for the blood collection. The tourniquet is then removed, the needle is withdrawn, and a gauze pad is placed over the site. The practitioner must never withdraw the needle without removing the tourniquet. After needle removal, the patient can be instructed to relax his or her fist. Anticoagulant agents can be added to the blood sample; these agents preserve blood cell morphology while preventing blood coagulation. Contaminated materials are disposed of in hard-cased containers (sharps container). The patient should be continuously monitored for a few minutes after blood sampling for possible syncope.

HEMATOLOGY

Complete Blood Count

In general, the complete blood count (CBC) provides an overview of hematologic abnormalities that reflect systemic disease states. The CBC is particularly useful in the evaluation of anemia and leukemia, although hematologic changes may occur in infection and inflammation. Any patient who shows clinical signs of anemia (i.e., dilated retinal veins, retinal hemorrhaging, retinal edema, and exudates) or leukemia (i.e., infiltration and hemorrhages of the lids and conjunctiva) needs a hematologic evaluation including a CBC.

The CBC includes the red blood cell (RBC) count, hemoglobin (Hb or Hgb) measurement, hematocrit (Hct), red blood cell indices, white blood cell (WBC) count and differential (diff) count, blood smear, and platelet count. Inexpensive, easy, and rapidly performed as a screening test, the CBC is ordered from the laboratory on a hematology order form. The blood is obtained by venipuncture or fingerstick, and results are available within a few hours.

Red Blood Cell Count

The RBCs, or erythrocytes, are created in the bone marrow and act to transport oxygen and carbon dioxide and help control the pH of the blood. The RBC count is the number of circulating RBCs in 1 mm^3 of peripheral venous blood. Erythropoietic dysfunction or blood loss is indicated by results outside the normal range of 4.6 to 6.2 million/mm^3. A decrease in RBCs occurs in drug use, tumors, anemia, hemorrhage, pregnancy, dietary deficiency, genetic disorders, and bone marrow failure. Ocular effects occur in severe cases of anemia and include hyphema, hard exudates, conjunctival pallor, flame-shaped hemorrhages, and dot and blot hemorrhages.

Polycythemia is seen as an increase in RBCs and may be caused by high altitude, congenital heart disease, polycythemia vera, and dehydration. Polycythemia may have ocular manifestations, including markedly dilated and tortuous retinal veins as well as disc edema. The normal lifespan of a RBC is 120 days, and when age or cell membrane damage causes the RBC to be lysed, it will be removed from circulation by the spleen. A shortened lifespan of an RBC may be the result of artificial heart valves and peripheral vascular atherosclerotic plaques.

Hemoglobin

The Hgb concentration is the total amount of Hgb in the peripheral blood, and reflects the total number of RBCs in the blood. Hgb is the oxygen and carbon dioxide-carrying pigment of the red blood cell. Its level is reported as grams per 100 ml (dl) of blood. The normal hemoglobin level in men is 14 to 18 g/dl and in women is 12 to 16 g/dl.

Decreased levels of Hgb can indicate pregnancy, a reduced number of RBCs (anemia), and hemoglobinopathies such as sickle cell disease. Anemic retinopathy may occur in severe cases of a reduced Hgb level. Elevated Hgb is typical in patients living at high altitudes and in cases of polycythemia vera, chronic obstructive pulmonary disease and congestive heart failure, and may be seen in patients with typical polycythemia-type retinopathy. The Hgb measurement is ordered through hematology.

Hematocrit

The Hct is the packed red blood cell volume, and reflects the percentage of the total blood volume that is made up of red blood cells. This measurement closely reflects the Hgb and RBC values. The normal Hct is 42% to 52% in males and 37% to 47% in females. Reduced levels of Hct indicate anemia, and elevated levels may be caused by erythrocytosis, which is an absolute increase in red blood cell mass, and heart failure or chronic anoxia. The Hct and Hgb are most often ordered together as an "H and H" through the hematology lab.

Red Blood Cell Indices

These erythrocyte parameters help diagnose specific anemias. To correctly diagnose the various types of anemias, the relationship between the size, number, and Hgb content of the erythrocytes must be established. To this end, an examination of the stained peripheral blood (collected by venipuncture or fingerstick method) reveals the red blood cell characteristics. These indices include the mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red blood cell distribution width (RDW).

Mean Corpuscular Volume

The MCV index provides information on the size of the RBC. Cell size may be normocytic (normal RBC size), microcytic (smaller than normal RBC size), or macrocytic (larger than normal RBC size). The MCV measures the average volume of a single erythrocyte, expressed as cubic micrometers per red blood cell. The normal value is 80 to 95 μm^3, and the value may be increased in liver disease, alcoholism, and vitamin B_{12} and folic acid deficiency (megaloblastic anemia). The value is decreased in anemia because of iron deficiency and thalassemia.

Mean Corpuscular Hemoglobin

The MCH index provides information on the amount, or weight, of hemoglobin in an individual RBC. This value closely resembles the MCV number because macrocytic RBCs tend to have more Hgb, and microcytic RBCs are smaller and so have less Hgb. The normal MCH value is 27 to 31 pg.

Mean Corpuscular Hemoglobin Concentration

The MCHC is a measurement of the average concentration of hemoglobin within a single RBC. The normal values are 32 to 36 g/dl (or 32% to 36%). A low value indicates lower hemoglobin concentration, a pale RBC, and is described as hypochromic. A normal hemoglobin concentration produces a normal-appearing RBC color and is normochromic. Elevation of hemoglobin concentration above 37 g/dl is impossible because of size constraints. Therefore, a hyperchromic condition does not exist. Low levels are seen in iron deficiency and thalassemia. Anemias that are normochromic and normocytic in nature are most often caused by tumor, iron deficiency, acute blood loss, and aplastic anemia (caused by, for example, chloramphenicol toxicosis). Microcytic, normochromic anemia is most commonly caused by renal disease. Microcytic, hypochromic anemia is commonly caused by thalassemia, lead poisoning, and iron deficiency. Finally, macrocytic, normochromic anemia can be secondary to a vitamin B_{12} or folic acid deficiency and chemotherapy.

Red Blood Cell Distribution Width

The RDW is a measurement of variation in RBC size. Anisocytosis is a type of anemia characterized by a wide range of RBC sizes. An increase in RDW can occur in iron-deficiency and B_{12}-deficiency anemia, sickle cell disease, and posthemorrhagic anemia.

White Blood Cell Count

The WBC count measures the total number of leukocytes, or WBCs, in 1 µl of peripheral venous blood. The normal WBC count is between 4500 and 10,000 cells/mm^3. An elevation in the number of WBCs is known as

leukocytosis and is most often caused by infection involving a bacterial cause. Other causes of leukocytosis include trauma, stress, neoplasm, and inflammation. A decrease in the WBC count is called leukopenia and may arise from bone marrow failure after chemotherapy or radiation therapy, acute viral infections, starvation, drugs, and stress. The WBC count gives only the total number of leukocytes and is of limited value in diagnosis. Significant additional information is provided when a differential count of the various leukocyte types is performed. Collection of a WBC count is by venipuncture or fingerstick and is ordered through hematology, usually as part of a CBC.

Differential

The differential count identifies and measures the percentages of the various types of leukocytes. Because the WBC count yields only the total number of WBCs, it may have limited value in the differential diagnosis of anemias, leukemias, infections, and inflammations. To this end, the various types of leukocytes are differentiated and counted. The leukocytes include the granulocytes, or polymorphonuclear leukocytes (neutrophils, basophils, and eosinophils), and the nongranulocytes (the lymphocytes and monocytes). Changes in each of these leukocytes may indicate certain disease states and are of great value in the differential diagnosis. The function of the various types of leukocytes is usually to fight infection and to react against foreign antigens. Elevated levels of one particular leukocyte will cause a drop in levels of other types of WBCs. The test is ordered through hematology and the sample is collected by fingerstick or venipuncture.

Neutrophils. These granulomatous leukocytes compose 56% of the total WBC and are the most abundant of all the cells seen. A reduction in the number of neutrophils can occur in acute viral infections and starvation. An elevation in the number of neutrophils can be caused by bacterial infection, trauma, inflammation, tumors, and drugs. Neutrophils are produced in 1-2 weeks within the bone marrow from stem cells and exist for approximately 6 hours. These leukocytes act to destroy bacterial microorganisms by phagocytosis.

Basophils. These granulomatous mast cells compose 1.5% of the total number of leukocytes and are involved in allergic reactions. Basophils do not react to bacterial or viral infections but are involved in antibody-antigen reactions by releasing heparin. Parasitic infestation may cause a rise in the basophil level.

Eosinophils. Composing as much as 8% of the total number of WBCs, these granulomatous leukocytes are elevated in allergic reactions or parasitic disease. A reduction in eosinophils is seen when the allergic response abates and in stress reactions.

Lymphocytes. These nongranuloctyes, or agranulocytes, compose 19% to 48% of the WBCs and are formed in the lymph nodes and thymus gland. Lymphocytes mediate chronic bacterial infections and acute viral infections. The two types of lymphocytes are T cells and B cells. The T cells participate in cellular-type immune reactions, and the B cells are primarily involved with antibody production (humoral immunity). The differential counts the T cells and B cells as a total number of lymphocytes and does not differentiate them. Elevations in the lymphocyte level may occur in chronic lymphocytic leukemia and in viral infections, such as measles, chickenpox, and mononucleosis.

Monocytes. These phagocytic nongranulocytes fight bacteria much like neutrophils but are produced more rapidly and circulate for a longer period of time. Monocytes compose from 3.4% to 9% of the total WBCs.

Platelet Count

Because the platelets, or thrombocytes, are necessary for blood coagulation, the platelet count helps in the evaluation of bleeding disorders. The platelet count is the number of thrombocytes in a cubic milliliter of blood. The normal platelet count is between 150,000 and 400,000/mm^3. A low platelet count is referred to as thrombocytopenia, and may be caused by immunologic response, drugs, transfusion, or infection. A rise in thrombocytes, or thrombocytosis, may be the result of iron deficiency, malignant disease, or myeloproliferative syndromes.

BLOOD CHEMISTRY

Biochemical Profile

Any variety of blood chemicals may be analyzed to help in the diagnosis and management of disease states. Twelve of the most common and meaningful of these chemistry tests can be performed by ordering a chemistry panel, also known as the sequential (or simultaneous) multiple analysis (SMA-12). With the advent of sophisticated instrumentation, the physician is encouraged to order the most appropriate tests necessary to profile the patient. The SMA-12, on the other hand, is useful as a multiple organ system survey. The test may include the following general screenings: enzymes [usually alkaline phosphatase (ALP), lactic dehyrogenase (LD), and serum glutamic-pyruvic transaminase], waste products [usually bilirubin, blood urea nitrogen (BUN), creatinine, and uric acid], nutritional components (albumin and total protein) and miscellaneous chemicals (most often calcium, phosphorous, total cholesterol, and serum glucose).

Clinical Enzymology

Enzymes are protein catalysts that help to speed most of the chemical reactions of the body. Enzymes are found in all tissues and are found in elevated amounts in the blood when tissue or organ injury exists. When

damaged or stressed, certain tissues will release specific enzymes into the serum, and the detection of these elevated levels pinpoints the organ system involved in the disease.

Alkaline Phosphatase

Critical in the study of bone diseases, elevations in ALP are seen in patients with healing fractures and bone tumors. In addition, elevated levels of ALP may be seen in liver problems such as jaundice or space-occupying lesions. ALP can be elevated in pregnancy, in some cases of sarcoidosis, and in childhood because of bone growth.

Aminotransferases (Transaminases)

Aspartate aminotransferase (AST, formerly glutamate oxaloacetate transaminase), and alanine aminotransferase (ALT, formerly serum glutamate pyruvate transaminase), are both most often markedly elevated in liver disease. Elevations are seen in viral hepatitis, cirrhosis, and metastatic carcinoma to the liver. Persistent elevation in ALT is useful in the diagnosis of hepatitis C. In a patient with acute myocardial infarction, the level of AST may be elevated within 12 hours of the time of infarction, and peaks on the second day. Normal levels return by the fifth day. In such patients, the level of ALT remains typically normal, because ALT is elevated primarily in liver disease.

Lactate Dehydrogenase

LD is found throughout the tissues of the body, particularly in the heart, kidney, liver and muscle. Most often, elevations in LD are used to diagnose myocardial infarction and kidney and liver dysfunction. In patients with myocardial infarction, LD elevates within 24 hours of the onset of the heart attack, peaks in 3 days (as compared with AST which peaks 2 days postinfarction), and persists for a week or two.

Creatine Kinase

Also known as creatine phospokinase, or CPK, CK is concentrated in high levels in the skeletal muscle, heart, and brain. It is not found in the liver, so high amounts may indicate myocardial infarction but not liver disease. After myocardial infarction, CK rises quickly (within 6 hours) and peaks in 24 hours, so it is most useful in the acute diagnosis of heart attack. AST then peaks in 48 hours, and LD peaks in 72 hours postinfarction. CK is the main cardiac enzyme studied in possible heart attack. Myoglobin is an oxygen-binding protein that, when elevated, indicates damage to the myocardium three hours after myocardial infarction. It is not considered part of SMA testing, but it is more specific than and elevates earlier than the CK test. New and promising lab studies into muscle proteins called troponins have revealed them to be a valuable asset in establishing the diagnosis of myocardial infarction and in predicting future cardiac events. This test is used on patients with chest pain and unstable angina to establish true myocardial damage. The cardiac-specific troponin test is more specific than the CK test in the determination of cardiac muscle injury.

Angiotensin-converting Enzyme

Angiotensin-converting enzyme (ACE) is found mainly in the lung and liver. Serum elevations of ACE are found in patients with sarcoidosis, and significant levels are achieved in pulmonary sarcoid. Inactive sarcoid rarely produces elevated ACE levels. Active tuberculosis infection of the lung does not produce elevated ACE levels. Cirrhosis of the liver may produce elevated ACE levels.

Waste Products

Screening for renal function using levels of blood urea nitrogen (BUN) and nonprotein nitrogenous compounds (creatine, creatinine, and uric acid) is a quick and inexpensive way to detect renal failure. In addition, BUN can be used to detect liver disease. Bilirubin is a pigment and is used as a test of liver function.

Blood Urea Nitrogen

The BUN test measures the amount of urea nitrogen in the blood. Ingested proteins are broken down into amino acids, which are metabolized in the liver-forming urea, which is then transported by the blood to the kidney for excretion. Because urea is inadequately excreted, elevated BUN (azotemia) can indicate renal disease, a high-protein diet, and dehydration. Low levels of BUN occur in liver disease because the synthesis of urea depends on the liver. The BUN is used with the creatinine test to determine renal function.

Creatinine

Creatinine is excreted entirely by the kidneys; therefore, its level reflects renal function. Abnormal elevations indicate impairment of renal excretion, as would occur in glomerulonephritis and urinary obstruction. The creatinine level is not influenced heavily by the liver. In addition, creatinine elevation tends to indicate chronic kidney disease, and elevated BUN indicates acute renal disease.

Uric Acid

Uric acid is a major product of purine catabolism. Uric acid is mostly excreted by the kidneys, although a smaller amount is excreted in the intestinal tract. If uric acid is overproduced or excretion is decreased, a state of hyperuricemia will exist, with an elevated serum uric acid level. Overproduction can be a result of cancer or a catabolic enzyme deficiency. A decrease in excretion is a result of renal failure. Elevated serum

uric acid levels can result in gout and may be associated with diabetes mellitus, hypertension, atherosclerosis, and myocardial infarction. Gout may be associated with deposits of uric acid crystals in the anterior stroma of the cornea resulting in reduced visual acuity. Low levels of serum uric acid occur in Wilson's disease.

Bilirubin

Bilirubin is a bile pigment, the breakdown product of erythrocyte hemoglobin. This substance forms in the liver and may circulate in the plasma bound to albumin. Bilirubin is a waste product and must be eliminated from the liver into the bowel. Elevated bilirubin can occur in hepatitis, cirrhosis, alcoholism, and some anemias. Patients who are seen with jaundice, with possible yellowing of the conjunctiva, have high concentrations of bilirubin. The most common clinical disorder associated with jaundice is hepatitis, which causes obstruction of the bile ducts because of gallstones or a tumor. Jaundice may produce yellowing of the conjunctiva.

Miscellaneous Tests

These tests analyze four chemical constituents of the sera that reflect the general health of the patient and screen for systemic diseases. These tests include calcium, phosphorus, glucose, and total cholesterol.

Calcium

Calcium is essential for heart, muscle, and nerve function, and blood coagulation. Calcium is used to test parathyroid function, monitor renal failure, and assess calcium metabolism. Elevated calcium levels occur in carcinoma, alcoholic dehydration, sarcoidosis, tuberculosis, histoplasmosis, leukemia, and hyperthyroidism. In fact, about 25% of individuals with sarcoidosis have elevated calcium levels. Low calcium levels are seen in malnutrition and low protein levels, because calcium is bound to serum albumin. For this reason, serum calcium and serum albumin should always be measured at the same time. Hypercalcemia is confirmed when calcium levels are elevated on three consecutive tests. Eye patients who are seen with corneal band keratopathy, lithiasis of the conjunctiva, juvenile xanthelasma of the lids, and corneal arcus juvenilis may have abnormal calcium levels and should have a serum test.

Phosphorus

Phosphorus, an inorganic blood compound in the form of phosphate, is found mostly in the human skeleton bound to calcium. The remainder is in the serum as a phosphate salt. Elevated levels of phosphorus may be found in some patients with sarcoidosis and diabetic ketosis. Decreased levels are found in acute alcoholism and malabsorption syndrome. The phosphorus level is often evaluated relative to the calcium level, and as the level of one goes up the other goes down.

Total Cholesterol

No longer considered an adequate evaluation of serum lipid levels, elevated total cholesterol levels are nonetheless associated with increased risk of coronary artery disease in middle-aged men. Recent studies support the observation that elevated total cholesterol in both men and women is linked to an increased risk of a vascular event. It is the most significant lipid related to arteriosclerotic disease. For appropriate determination of relevant cholesterol levels, it is recommended that low density and high-density lipoprotein cholesterol also be determined as part of a lipid profile. Eye patients with pronounced arcus juvenilis and retinal Hollenhorst plaques should have cholesterol levels measured in an effort to determine the risk of coronary artery disease and other vascular diseases in these patients. Cholesterol is both ingested and synthesized in the liver. It is used for fat transport, cell membrane formation, and steroid and sex hormone formation. The clinician should corroborate elevated cholesterol levels by averaging the results of multiple studies when determining the risk assessment for a vascular event. Low cholesterol is rare and is an indicator of severe liver disease.

Glucose

Glucose is a sugar that is metabolized within cells to produce glycogen, amino acids, and fatty acids. Glucose enters the cells from the surrounding blood by binding to the hormone insulin. This process occurs after a meal, when serum glucose rises. In the fasting state, serum glucose levels are low, which stimulates the production of glucagon. Glucagon is a hormone that raises serum glucose levels; thus an elaborate feedback mechanism exists that controls the level of glucose in the blood. A low serum level of glucose is undesirable, because it means that cells cannot get the nutrition they need for metabolism. A high serum level of glucose is also undesirable, because it means that glucose is not entering the cells. To achieve the appropriate blood glucose level, an inverse relationship exists between the amount of secreted insulin and glucagon. For the fasting blood glucose level, the patient should be instructed to fast for 8 hours before the test. Serum glucose is useful in the diagnosis of diabetes mellitus. Patients with an unexplained retinopathy, and any patient with a sudden shift in refractive error, increase in hunger (polyphagia), increase in thirst (polydipsia), or increase in urination (polyurea), should be given a fasting blood glucose test. Elevated serum glucose can also occur during

anesthesia, cerebrovascular accident, myocardial infarction, pregnancy and certain medications.

Nutritional Status

Total serum protein and serum albumin are the most common SMA-12 tests used to monitor the nutritional status of the patient.

Total Serum Protein

Proteins are used as co-transporters and buffers in the blood, and they are constituents of muscles, enzymes, and hormones. The protein level and the albumin level are used to evaluate a patient's nutritional status, liver function, and nephrotic syndromes. Patients who are seen with nutritional-type amblyopia, alcoholism, or anorexia warrant a protein level determination.

Serum Albumin

A specific protein, albumin is formed in the liver and makes up the majority of the total protein. Its major function in the blood is to maintain colloidal osmotic pressure. A good indicator of nutritional status, albumin is also useful in the evaluation of burns, liver disease, kidney disease, heart disease, and chronic alcoholism.

INFLAMMATORY MARKERS

Erythrocyte Sedimentation Rate

The protein content of the plasma, mostly fibrinogen, increases in response to acute and chronic inflammation. This process causes the erythrocytes, or red blood cells, to bind to each other in clumps and settle out of solution in a container. The erythrocyte sedimentation rate (ESR) measures the rate at which the RBCs settle out of solution during a specified period of time. The causes of an increased ESR include some infections, collagen-vascular diseases, inflammatory diseases, and tissue damage from myocardial infarction. The ESR occurs as a reaction to an existing inflammatory disorder, and so it is considered an "acute-phase" protein. It is fairly sensitive, but very nonspecific, and so it is not diagnostic for any particular disorder. ESR is, however, a reliable indicator of therapy and can be used to measure the effectiveness of treatment. ESR is especially useful in the diagnosis of temporal arteritis (giant-cell arteritis) and the uveitis-related systemic diseases.

C-Reactive Protein

Like the ESR, the C-reactive protein (CRP) is an acute-phase protein. CRP is, however, more sensitive than the ESR rate, and so responds more quickly to the presence of inflammation, and disappears faster on resolution of the inflammation. The high-sensitivity CRP (hsCRP) test measures small amounts of CRP in the blood. The hsCRP is useful in assessing the risk for cardiac disease. CRP is useful in the diagnosis of inflammatory diseases such as rheumatoid arthritis, Reiter's syndrome, and Crohn's disease. Recent research points to the effectiveness of measuring CRP to help predict the likelihood of a major vascular event. Elevated CRP is nonspecific and thus does not indicate any particular disorder. A positive result does, however, indicate the presence of an inflammatory disease. A protein formed by antigen-immune complexes, CRP is found in tissue damaged by trauma and is produced when pathogens, such as bacteria and viruses, initiate an immune response. CRP has been shown to be useful in the evaluation of myocardial infarction, peaking later than CK, and if values remain high, it may indicate chronic heart-tissue damage.

URINALYSIS

The normal patient excretes about 1 L of urine daily. Waste products of metabolism are carried out of the body in the urine, as is important information related to the presence of disease. To this end, urinalysis provides a technique for the urine to help in the evaluation and management of disorders.

Urinalysis actually encompasses several tests that can be performed in the laboratory, office, or home. Urinalysis is divided into macroscopic testing and microscopic testing. Macroscopic testing includes an evaluation of the sample's appearance, specific gravity, color, and pH. Also included are tests to detect the presence of protein, glucose, ketone bodies, bilirubin, nitrite, occult blood, leukocyte esterase, and urobilinogen. Microscopic studies include tests of the urine sediment following centrifugation of the sample to look for red or white blood cells, bacterial colonies, casts, and crystals.

A total urinalysis is obtained on a clean-catch, midstream specimen. The urine sample is then split into two parts, with one sent to the laboratory for analysis and the other for culturing

Macroscopic Evaluation

Appearance

The macroscopic evaluation begins with the appearance of the urine. Because a wide range of urine constituent concentrations exists, urine specimens have a wide variety of characteristic colors, from pale yellow (dilute urine) to dark amber (concentrated urine). The normal color of urine is a result of metabolic breakdown products such as bile, as well as pigments found in the patient's diet. Evaluation of the appearance of urine includes not only color but also an inspection for stringy mucus, which may be the result of infection.

Blood in the urine is called hematuria and is a significant finding necessitating a medical evaluation. Dark red urine indicates bleeding from the kidney, and bright red urine results from bleeding in the lower urinary tract. Dark brown urine may occur in jaundice, indicating possible liver disease.

Odor

Volatile acids cause the typical urine scent. A strong, sweet-smelling urine can occur in diabetic ketoacidosis. A urinary tract infection may produce a pungent and rancid smell.

Specific Gravity

The specific gravity of the urine sample may reflect the degree of hydration present. It is an indicator of renal function and is dependent on the urine volume and presence of excreted solids. Normal urine-specific gravity is approximately 1.020.

Urine Volume

The volume of urine typically increases in uncontrolled diabetes mellitus. Patients with a complaint of polyuria should be evaluated for diabetes.

Dipstick Testing

Urine must be collected in clean, usually disposable, containers. The patient is asked to void into the container after following any specific instructions, such as fasting, or collecting multiple samples for 24 hours.

The use of dipsticks containing a number of tests on each stick expedites macroscopic urinalysis. These tests include glucose, protein, ketones, blood, pH, bile, bilirubin, nitrite, leukocyte esterase, and urobilinogen.

Glucose

Normal urine does not contain enough glucose to yield a positive result on a dipstick. A positive urine glucose finding should therefore be treated as an abnormality, and an evaluation to rule out diabetes mellitus is mandatory. Because a positive urine glucose test does not confirm the presence of the disease, serum glucose remains a more meaningful test than urine glucose testing alone. This is a significant fact when a clinician is considering in-office glucose testing of patients with diabetic retinopathy or neuropathy.

Protein

Protein found in the urine (proteinuria) is an important indicator of renal disease. The protein, when found in the urine, is usually albumin. The list of disorders that cause proteinuria includes renal failure, glomerulonephritis, systemic lupus erythematosus, and many others. Proteinuria appears early in renal disease and may be the only clinical sign of the abnormality.

Ketone Bodies

Ketone bodies are intermediates of fat metabolism formed in the liver. Testing for ketone bodies is important in diabetics, children, pregnancy, all hospital admissions, and presurgical evaluations. Large amounts (ketonuria) occur in diabetic ketoacidosis. Ketones occur when fat instead of carbohydrate is used for energy. The presence of ketone bodies in the urine of a patient with diabetes indicates that the patient is not adequately controlled.

Blood

Blood in the urine (hematuria) may be detected visually as a smoky brown-appearing sample, chemically by a dipstick, or microscopically. Hematuria is usually caused by urinary tract disease, and occult (hidden) blood may be the result of any number of renal disorders.

pH

Although it can vary widely, the normal pH of urine is usually between 5.0 and 8.5. Changes in the pH value may be caused, for example, by a urinary tract infection, which can cause an alkaline shift (e.g., 9.0).

Bile

Bilirubin is formed from hemoglobin, bound to serum protein, and carried to the liver for processing. Bile is then produced and excreted into the intestine. An increase in bilirubin occurs when chemicals or viruses interfere with liver function.

Urine Urobilinogen and Bilirubin

Urobilinogen and bilirubin form from hemoglobin metabolism and are both considered bile pigments. Both are tested by dipstick. Bilirubin can appear in the urine in hepatitis, bile duct obstruction, and chemical injury to the liver. Elevated urobilinogen occurs in jaundice and cirrhosis.

Leukocyte Esterase (WBC Esterase)

A positive test indicates white blood cells in the urine, which is an indicator of urinary tract infection.

Nitrites

The nitrite test is positive in cases of urinary tract infection. Bacteria produce an enzyme called reductase, which reduces urinary nitrates to nitrites that are subsequently detected by this test.

Microscopic Evaluation

Urine can be centrifuged and the sediment examined for casts, cells, crystals, and bacteria. Casts usually indicate renal disease. Red and white blood cells indicate

hematuria or infection. Crystals are usually a sign of imminent renal stone formation.

Casts

These bits of congealed protein form a plug within the kidney tubule and then are washed into the urine. Casts can be seen only microscopically. Casts of red blood cells usually indicate glomerular inflammation or a renal vascular disorder.

Cells

The finding of red cells in the urine may indicate exercise, tumors, kidney trauma, passage of stones, and renal calculi (such as may occur when patients are taking certain carbonic anhydrase inhibitors). White blood cells indicate infection within the urinary tract.

Urinalysis in Eye Care

Urinalysis is an effective screening test for renal and hepatobiliary function, and for glucose. Macroscopic evaluation of the urine is easily performed in the private office setting by use of the dipstick. The optometrist should ask his or her local laboratory to demonstrate the proper dipstick technique and resulting interpretation.

The dipstick technique uses any number of chemical strips containing reagent tests that are sensitive to compounds present in the urine. These strips are dipped into the urine sample, and a certain amount of time is allowed for color transformation of the reagents. These colors are then compared with a normal standard color chart. Dipsticks may be purchased from a local laboratory or medical supply house.

Microscopic evaluation of the urine is performed if the dipstick is positive for occult blood, protein, or other factors. Microscopic evaluation requires a trained laboratory technician with experience in urinalysis.

If a positive result is discovered in the office, the patient should be referred to his primary health care provider, along with the results of the urinalysis and a report of any significant eye findings.

CLINICAL DIAGNOSIS BY LABORATORY METHODS

The diagnosis of systemic diseases is aided by the use of laboratory testing. In some cases, the clinical entity may produce overt signs and symptoms that point to a specific diagnosis. In these cases laboratory analysis may be used to help confirm or eliminate a tentative diagnosis. The systemic disease may be occult and thus produce minimal symptoms or signs, and so laboratory testing can be used to detect early pathology and help develop a differential diagnosis. Clinical diagnosis by laboratory methods is of particular importance to the clinician faced with detecting an underlying systemic disease, as in cases of uveitis. The following text gives a list of systemic disorders commonly associated with ocular conditions and the laboratory tests used to help confirm their presence. For a complete diagnostic protocol on each of the diseases noted here, refer to Part II of this text.

Inflammatory Disease

Inflammation is a basic physiological response that occurs in most disease states. Inflammatory markers, which are laboratory tests that determine the presence of inflammation, are known as acute-phase indicators. In addition to the ESR and CRP tests described in the preceding text, the alpha-1 antitrypsin test is also an acute-phase protein measurement. The Westergren method is the most common of the ESR tests, and measures the rate at which erythrocytes settle out of solution in a 1-hour period. In general, the higher the rate, the more significant the inflammation. As the inflammation resolves, the sedimentation rate goes down. A protein produced by the liver during inflammatory disease states, CRP is more sensitive than the ESR and tends to be more reactive than other acute-phase indicators. It is useful in the diagnosis of acute myocardial infarction and recently is being investigated as a better prognosticator for major vascular events than lipoprotein levels. Alpha 1-antitrypsin (A1AT) is an acute-phase reactant that elevates in cases of inflammation. A1AT is nonspecific and indicates generalized inflammation.

Collagen-Vascular Disease

Rheumatoid Arthritis

This chronic inflammatory disease affecting the synovial joints is produced by abnormal immunoglobulins (from lymphocytes) that react with immunoglobulins from the synovial tissue. These immune complexes cause inflammation in the joints. The immunoglobulin IgM that reacts in this case is known as rheumatoid factor (RF), and is a test to detect this antibody. Of patients with rheumatoid arthritis, 80% are positive for RF. Positive RF is also found in some cases of systemic lupus erythematosus and Sjögren's syndrome. In cases of anterior uveitis of unknown origin, it is useful to order an RF test, because rheumatoid arthritis has been shown to rarely be associated with anterior chamber inflammation. The ESR and CRP are increased in nearly all cases of RA. The presence of RA is confirmed by synovial fluid analysis.

Juvenile Rheumatoid Arthritis

Juvenile rheumatoid arthritis (JRA) is the most common connective tissue disease in childhood and differs from the adult form in many ways. The classic signs

and symptoms include a destructive arthritis accompanied by high, spiking fevers and lymphadenopathy. Laboratory results usually reveal very high WBC counts, negative RF and antinuclear antibody (ANA), and an elevated ESR and CRP. Chronic JRA may yield a positive ANA in some cases.

Systemic Lupus Erythematosus

In systemic lupus erythematosus (SLE), tissue and cellular destruction exists that is caused by pathogenic autoantibodies and immune complexes. Of the thirteen laboratory tests used currently to evaluate a suspected case of lupus, four significant laboratory tests can help confirm the presence of SLE. All of these tests involve the detection of antibodies. (1) The anticardiolipin (aCL) antibodies test detects the presence of IgG and IgM antibodies to cardiolipin, which are found in approximately 40% of patients with lupus. (2) The antiDNA antibody test is used to detect two types of antiDNA antibodies. The antidouble-stranded DNA (anti-dsDNA) test is useful in detecting SLE. The antisingle-stranded DNA test is useful in detecting other autoimmune diseases. The titer levels of the anti-DNA antibody test coincide with the severity of the disease. (3) The antiextractable nuclear antigen (antiENA) test detects antinuclear antibodies that react to certain nuclear antigens of RNA and protein. (4) Perhaps the most often used and best test is the ANA test, which detects a group of antinuclear antibodies that reflect the presence of autoimmune disease. A negative ANA test indicates the absence of autoimmune disease and therefore rules out SLE. The test is positive in approximately 95% of lupus cases, but a positive result does not confirm SLE because other conditions can induce antinuclear antibodies.

Sjögren's Syndrome

Sjögren's syndrome is characterized by a progressive loss of lacrimal and salivary exocrine glands. This immunological disease results in dryness of the mouth, eyes, and nose. The Sjögren's antibody tests [antiSS-A (RO), antiSS-B (LA), and anti-SS-C] detect antinuclear antibodies that react to nuclear antigens and confirm the diagnosis.

The Spondyloarthropathies

Among this group of disorders are ankylosing spondylitis (AS) and Reiter's syndrome, which can contribute to the presence of uveitis. AS is an inflammatory disorder that produces lesions at the site of the attachment of ligament to bone, most commonly around the pelvis and spine (sacroiliitis). Reiter's syndrome is now more commonly referred to as reactive arthritis (ReA) and refers to an acute, nonpurulent arthritis associated with an antecedent infection and characterized by distal joint inflammation. Of AS cases, 90% are positive for the human lymphocyte antigen B27 (HLA-B27) , and 75% are positive in cases of ReA. HLA-B27 exists on the surface of most cells and is easiest to detect on lymphocytes. Genetic determination can detect the presence of these antigens, because each gene controls the existence of the HLA-B27 antigen. The inflammatory markers of the ESR and the CRP test are elevated in most, but not all, cases of AS and ReA. The ANA is negative in both these disorders.

Temporal Arteritis (Giant-cell Arteritis)

A vasculitis of the medium-and-large arteries, giant-cell arteritis (GCA) can cause sudden visual loss as a result of ischemic optic neuropathy. The ESR and alkaline phosphatase levels are typically elevated. The disease is suspected in individuals who demonstrate fever, scalp pain, and tender temporal artery, and an elevated ESR. CRP has been shown to be even more sensitive in cases of GCA than the ESR. The presence of GCA is confirmed by a temporal artery biopsy. Other laboratory findings in GCA include an increase in plasma viscosity, a CBC that reveals anemia, increased thrombocyte count, and an increase in anticardiolipin antibodies.

Sarcoidosis

Sarcoidosis is a multisystem, granulomatous disease of unknown etiology that causes the deposition of granulomas and the derangement of normal tissue structure. Serum levels of ACE are elevated in two thirds of sarcoidoisis cases. ACE is used to determine the severity of sarcoidosis, its response to treatment, and to differentiate sarcoidoisis from other granulomatous diseases. ACE can also be used to differentiate an active from a dormant sarcoid. Hypercalcemia, or an elevated calcium level, is found in about 25% of sarcoidosis cases. The ESR and CRP are typically elevated in active cases of sarcoid. The gallium-67 scan uses radioactive gallium, which is injected intravenously followed by a total body scan at regular intervals. Gallium will become concentrated in areas of inflammation, including sarcoid-related granulomas. Most often these will be visualized on the scans in the lung fields or in the parotid and salivary glands.

Thyroid Disorders

Thyroxine (T_4) makes up 90% of thyroid hormone and the remainder is triiodothyronine (T_3). T_3 and T_4 are produced by the thyroid gland. The total T_4 test measures the total amount of T_4 present in a patient's blood. Hyperthyroidism would be detected as an elevated T_4, and low levels indicate hypothyroidism. The T_3 test also measures thyroid function and, along with T_4, can assist in determination of thyroid function. T_3

and T_4 are released by the thyroid under the influence of thyroid-stimulating hormone (TSH), which is released from the anterior pituitary gland. TSH is, in turn, influenced by the circulating levels of thyroid hormones as well as stimulation from thyroid-releasing hormone (TRH) from the hypothalamus. The TRH test involves the intravenous injection of TRH to assess the function of the pituitary gland by measuring the amount of TSH that is released. After TRH is injected, the pituitary should be stimulated to release thyroid-stimulating hormone (TSH). In cases of hyperthyroidism, in which circulating thyroid hormones are elevated, the injection of TRH will not cause an increase in TSH. TSH does not increase because elevated thyroid hormones directly suppress TSH at the level of the pituitary, and thus the injected TRH has no effect. In addition, the TRH test can help determine the cause of hypothyroidism, because a TRH test in a hypothalamic problem will result in a delayed rise in TSH, a pituitary problem results in no TSH release, and a thyroid problem results in a TSH level above normal. The TSH test can differentiate primary (thyroid-based) from secondary (hypothalamic or pituitary-based) hypothyroidism. The release of THS from the pituitary gland is stimulated by hypothalamic TRH, and this in turn influences the release of the thyroid hormones T_3 and T_4. Secondary hypothyroidism is caused by diseases of the hypothalamus or pituitary gland, and thus TSH levels can be reduced. This decrease in turn causes low levels of T_3 and T_4. Low levels of thyroid hormone and TSH therefore indicate a hypothalamic or pituitary problem, and low level of thyroid hormone with normal TSH indicates a thyroid problem. The TSH stimulation test is also useful in differentiating primary from secondary hypothyroidism. In this test, exogenous TSH is given to the patient. If the hypothyroidism is caused by a hypothalamic or pituitary problem (secondary hypothyroidism), the thyroid hormone T_4 should elevate in response to the hormone. If the hypothyroidism is the result of a thyroid problem (primary hypothyroidism), no increase in thyroid function should occur because the thyroid gland cannot respond no matter how much stimulation from the TSH it receives. Thyroglobulin is a thyroid hormone carrier in the blood and in the thyroid. When it acts as an immune-stimulating antigen, autoantibodies develop and react against the thyroid gland. The resulting thyroid inflammation and destruction is known as thyroiditis. Detection of this thyroid antibody is accomplished by the antithyroglobulin antibody test. The antithyroid peroxidase antibody (anti-TPO) test is performed in conjunction with the antithyroglobulin antibody test to allow for better specificity and sensitivity. The anti-TPO test detects an antibody for a section of the microsome in the thyroid cell. Thyroid-stimulating immunoglobulins (TSI) are a group of IgG antibodies that are directed against the site on the thyroid gland that binds with TSH. This TSH receptor site on the surface of the gland gets attacked by these antibodies, which can either act to stimulate the production of thyroid hormone, as in Graves' disease, or act to inhibit thyroid hormone production, as in Hashimoto's thyroiditis.

Atherogenic Heart Disease

The lipid profile is performed to help determine a person's risk for developing coronary artery disease. Lipoproteins are found in the plasma and help transport insoluble fats such as cholesterol and triglycerides. The lipid panel usually includes the levels of triglycerides, total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL) and very-low density lipoproteins (VLDL). Alpha-lipoproteins are HDLs and are transporters of cholesterol molecules. HDLs may be the primary means of getting cholesterol out of the peripheral tissues and into the liver and also may serve to prevent cellular uptake of cholesterol. High HDL levels thus may be a protective mechanism against cardiovascular disease. LDLs tend to deposit their rich cargo of cholesterol into the peripheral tissues, thus increasing the risk of coronary artery disease. The higher the LDL level, the greater the risk of atherosclerosis. LDL is difficult to measure directly, and so it is often derived by a mathematical formula. The VLDL is the main transporter of triglycerides and so an elevated VLDL is associated with an increased risk of coronary artery disease. Apolipoproteins are polypeptides that form proteins that in turn help lipid transport. APO-A is the major polypeptide component of HDL, and a low level of APO-A may be a better indicator of atherogenic risk than HDL. APO-B is the major polypeptide component of low-density lipoprotein, and may be a better indicator at high levels of atherosclerotic heart disease. Lipoprotein(a), when elevated, may be a significant prognosticator for atherosclerosis development. Evidence exists that in elevated levels, homocysteine (Hcy) increases the risk of atherogenic heart, cerebrovascular, and peripheral disease. This increased risk is the result of endothelial damage to the blood vessels. Hcy is measured by enzyme immunoassay.

Diabetes Mellitus

In addition to serum glucose testing described above, a 2-hour postprandial glucose (PPG) study can be run in which a meal acts as a glucose challenge. In this test the glucose levels of the patient are tested at defined intervals after a meal, and normally insulin will cause blood glucose levels to fall back to normal within 2 hours. In a diabetic, serum glucose remains elevated two hours after a meal. A similar test, the glucose tol-

erance test (OGTT), uses blood and urine testing to evaluate glucose levels before and after a standard oral load of glucose is ingested. Nondiabetic patients show a peak of serum glucose in 1-2 hours with no glucose spilling over into the urine. Diabetic patients will show elevated blood glucose for as long as 5 hours with detection of blood in their urine (urine glucose evaluation is discussed in the section on urine testing). A test that is useful to monitor diabetes treatment is the glycosylated hemoglobin (GHb) evaluation, which measures the amount of hemoglobin A1c (HbA1c) in the blood. It is a reflection of the average of the diabetic patient's blood glucose level for the past 100 to 120 days, the average lifespan of a red blood cell. The more glucose that a red blood cell was exposed to the higher the A1c, indicating worsening glucose control.

Infectious Diseases

HIV-AIDS

Serology tests to detect the antibodies to the virus that causes AIDS include the enzyme-linked immunosorbent assay (ELISA), Western blot, and immunofluorescence assay. ELISA tests for antibodies to the human T-lymphotrophic virus (also called type III, or HTLV-III) in the serum. Because ELISA detects antibodies and not viral antigens, it may take as long as 6 months after exposure for a person to show a positive result on the test. The sensitivity and specificity of this test is 99%. Appropriate protocols set up by the U.S. Public Health Service call for the determination of serological evidence of HIV infection only after repeated ELISA testings are positive and a Western blot or immunofluorescence assay validates the results. After the positive Western blot test, a newer test called the detuned ELISA can help determine whether the HIV infection occurred within the past 6 months. This finding can help determine the early course of treatment. If the Western blot is equivocal, then tests that can determine the presence of the virus itself can be implemented. These tests include the p24 antigen capture assay, which detects HIV viral particles (viral protein p24) in the peripheral blood of infected patients. New oral testing kits use noninvasive oral mucosal transudate (OMT) to easily identify infected individuals. The use of oral saliva is fast and efficient and should help diagnose HIV earlier, thus leading to reduced disease transmission. Urine testing is a noninvasive way to detect urine HIV-1 antibodies but has not reached wide acceptance at present. Most home kits continue to use fingerstick blood samples that are sent to a certified laboratory where ELISA and Western blot procedures are performed, and results are available in about a week.

Lyme Disease

This bacterial disease caused by the spirochete *Borrelia burgdorferi* is spread most commonly by the bite of several different tick species. The most sensitive way to determine a Lyme infection is by serological testing. These tests determine the presence of antibodies to the spirochete. IgM antibody levels peak from 21 to 42 days after infection after which they begin to decline. IgG antibodies to the spirochete take 6 months to react. Most often, the disease is treated before true serological testing confirms the infection. Antibiotic therapy may be given on recognition of clinical signs suggestive of Lyme infection, particularly if the tick is isolated and a rash was identified.

Syphilis

This bacterial disease is caused by the spirochete *Treponema pallidum* and is spread by sexual contact. Two groups of tests exist to determine a syphilis infection. The first group of tests, known collectively as STS, detects reagin (cardiolipin-lecithin-cholesterol antigen complex), a treponemal antibody in an infected individual. This is a nonspecific antibody, and so the test is not very sensitive. Known as the VDRL (venereal disease research laboratory) or Wassermann test, it is being replaced by the newer RPR (rapid plasma reagin). The RPR is the most common of the two tests, but the VDRL is still performed on samples of cerebral spinal fluid to detect neurosyphilis. Both the VDRL and the RPR have a high false-positive rate. The second group of tests confirms the infection when the STS is positive. These *Treponema* tests detect spirochetic antibodies directed against the organism itself. The FTA-ABS (fluorescent treponemal antibody test) tests for a more specific antibody than the STS group and so is more accurate. The FTA-ABS must be positive before a diagnosis of syphilis is made. Another treponemal antibody test, the MHA-TP (microhemagglutination assay for *T. pallidum*) has been replaced by the Serodia TP-PA test, which has been shown to be more sensitive for primary syphilis. The RPR will elevate and decline in response to the population of the spirochetes, while after infection the FTA will remain positive for the life of the patient.

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CHAPTER 5

Radiology

CHAPTER OUTLINE

The field of radiology began on November 8, 1895, when William Konrad Roentgen discovered that a certain apparatus caused a piece of cardboard that was coated with chemicals and lying nearby to glow in the dark. In addition, when he passed his hand in front of the cardboard he could see the bones of his fingers within the shadow of his hand.

He proposed that his apparatus, a cathode tube, produced waves of shorter wavelength than light, and could penetrate materials that are opaque to visible wavelengths. He called the rays of energy emitted by his apparatus "x-rays," and found that, like light energy, they could blacken a piece of photographic paper.

Days later he took his first medical radiograph, of his wife's hand. He submitted his findings on December 28, 1895, and announced the discovery of x-rays in a presentation on January 6, 1896. His results were published a week later.

Just 1 month after his announcement, the use of contrast medium to radiograph blood vessels was detailed in a paper by Hashek and Lindenthal. Within the year more than a thousand papers were published throughout the world on the new field of radiology. Roentgen received the first Nobel Prize in physics 6 years later.

THE X-RAY

Electromagnetic waves that have the ability to penetrate matter are known as x-rays (Figure 5-1). This form of radiant energy is produced when an electron beam bombards a tungsten target. Once produced the x-rays radiate in all directions unless reflected or absorbed by an intervening substance. X-rays are integral to the techniques of radiography, by causing the exposure of film, and fluoroscopy, by the excitation of fluorescent material (Figure 5-2).

Uninterrupted x-radiation causes photographic film to become blackened. This occurs because x-rays precipitate metallic silver within a gelatin emulsion (the film) contained inside a cassette. A fluorescent screen is also contained in the cassette and is activated by the x-rays. This screen produces light waves that act to reinforce the x-ray picture. This reinforcing technique is used so that a minimal amount of radiation is needed. When exposed to x-rays, the fluorescent screen emits light rays that, combined with the x-rays themselves, expose the film much faster than without the screen. This approach is faster and thus reduces exposure to dangerous radiation.

A film exposed to x-rays has complete precipitation of silver, and the developed film turns out black. An

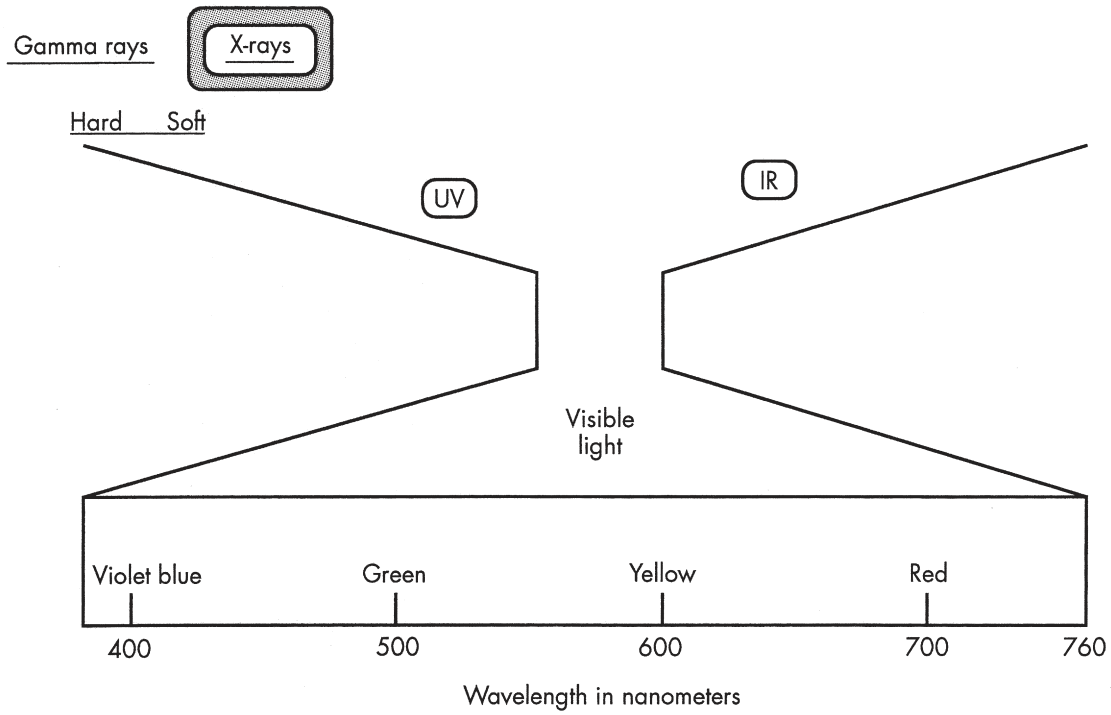

FIGURE 5-1 ■ Electromagnetic spectrum.

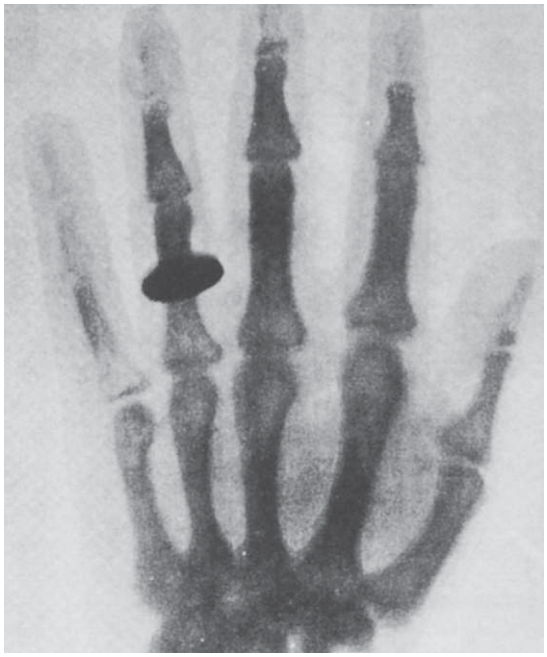

FIGURE 5-2 ■ Radiograph (actually a fluorography) of a hand.

object placed in the electromagnetic path reflects or absorbs the x-rays and prevents activation of the fluorescent screen. Without activation, no silver is precipitated, and the developed film turns out white. The denser the material, the lighter the exposure. For example, film exposed to x-rays with no intervening material becomes black, and metal absorbs x-rays (depending on its atomic number and thickness) to a degree that will render the film almost white. In the animal model, the denser the tissue, the lighter the image. Therefore, soft tissues appear dark gray, and dense bone, because of its calcium content, appears light gray (Figure 5-3).

High-density substances are known as radiopaque, and low-density substances are more transparent on the film and are called radiolucent. The most radiolucent substance is air, and the most radiopaque substance is steel. In the human body, substances in order from least dense (darkest exposure) to the most dense (lightest exposure) are fat, liver, vein, muscle, and bone (Figure 5-4).

DIAGNOSTIC IMAGING TECHNIQUES

Plain Films

Radiographs that are the result of only the differential beam absorption because of the various densities within various organs are known as plain films. This method is best used for the evaluation of bony structures, because soft tissues are poorly differentiated by this technique (Figure 5-5).

Various contrast media may be administered to overcome the absence of variety between tissue densities. Methylcellulose solution and gases, in the form of air, oxygen, and carbon dioxide, help differentiate

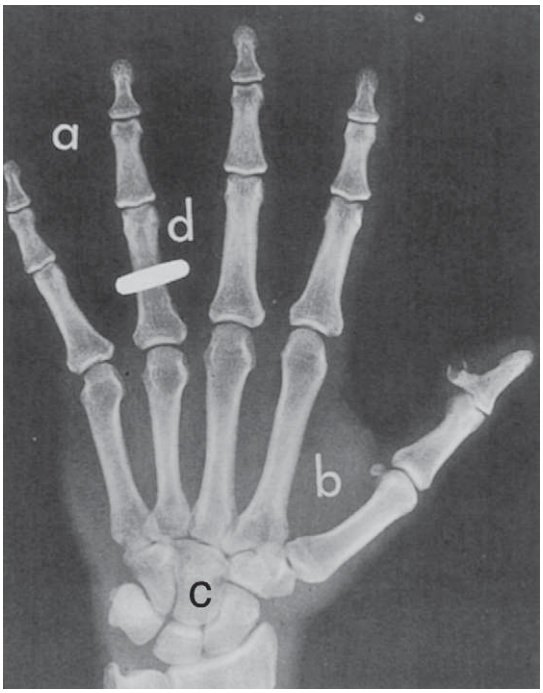

FIGURE 5-3 ■ Radiograph of a hand. Note that the gold ring on the third finger **(d)** totally blocks or absorbs all x-ray radiation and no exposure is seen. **b** shows the soft tissue of the hand. **c** demonstrates that dense bone appears light gray, and **a** shows that without absorption by an intervening material, the film turns black.

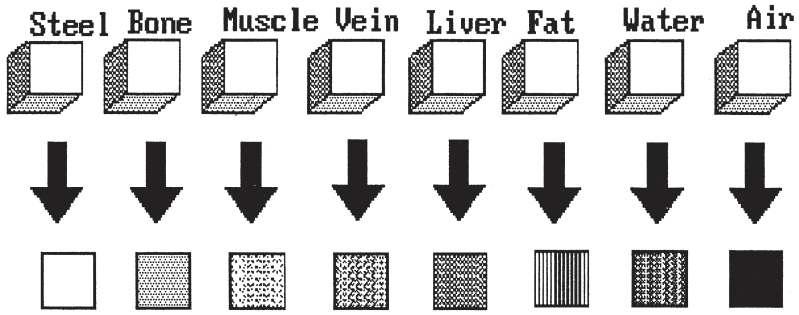

FIGURE 5-4 ■ Gray scale in order of densities of eight substances. At one end of the range are very dense substances such as steel and bone, which absorb most of the x-rays, and the film is white. The less dense substances at the other extreme, such as air, absorb none of the x-rays and the exposure is black. Human organs fall in between these two substances.

soft tissues. These compounds are known as negative contrast media because they are less dense than soft tissue. Barium and iodine compounds absorb x-rays more intensely than bone and are known as positive contrast material. These compounds are used with negative contrast media to enhance contrast between soft tissues. Depending on the tissue to be evaluated, a choice of contrast media is available. A significant number of patients are sensitive to contrast dyes, however, and so they must be screened for possible allergy.

Computed Tomography

Computed tomography (CT) is a computer-assisted imaging technique. Although the plain film images the entire depth of tissue that is exposed to x-rays, the CT has the capability of exposing a single plane, or "slice," of tissue. This remarkable achievement is the result of moving both the x-ray tube and the film plane opposite the patient. Both objects move around a "pivot point" located within the body of the patient—at the pivot point, no relative movement takes place. The

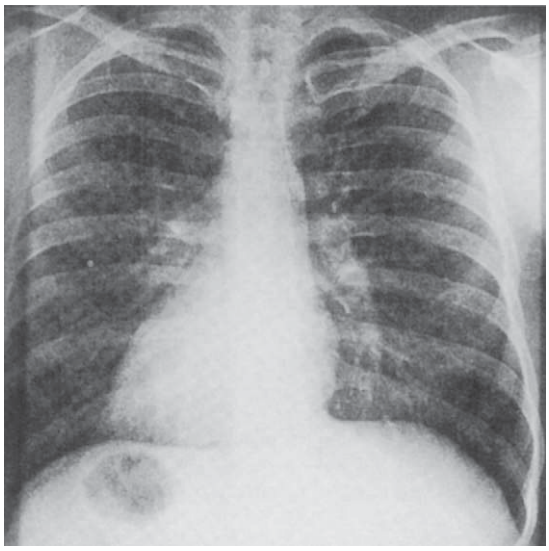

FIGURE 5-5 ■ Plain-film view of the chest. Note that bone is well discriminated, but soft tissue is poorly resolved.

movement of the tube and film blurs the intervening structures (Figure 5-6), but the tissue located at the pivot point photographs clearly. This technique is known as tomography (Figure 5-7).

In CT scanning, hundreds of detectors are placed in an arc centered at the focal spot of an x-ray emitter. The x-ray tube emits electromagnetic energy that is picked up by the detectors (Figure 5-8). The patient lays supine and the tube and detectors revolve around the patient. The patient is moved on the table in small increments through the apparatus, a procedure known as the "rotate-rotate" CT system. In the "rotate-fixed" system, the detectors are set up in a ring instead of an arc, and an x-ray tube is rotated within the ring of detectors. Computer programs are then used to convert the information received in each detector to form various shades of gray, and three-dimensional color images may then be produced.

CT is exceptional for differentiation of gray and white matter, cerebrospinal fluid (CSF), brain lesions, and swollen tissues. When compared with plain films, CT has the obvious advantage of creating a clearer image of the specific tissue under study. No confusing shadows are created from structures above and below the desired area.

The usual CT series of scans consists of contiguous 10-mm-thick slices through the region requested, but slices as thin as 1.5 mm can be obtained when finer detail is needed for diagnosis. CT scanners require only 1 to 10 seconds to complete a slice, and a patient who cannot hold his or her breath may have motion artifacts on the scan. Most patients can hold their breath for 5 seconds repeatedly; however, unconscious, very ill, or dyspneic patients and small children requiring CT studies may produce motion that degrades the image. Mild sedation and reassurance of the patient by the referring physician and the radiologist may help.

The patient should be forewarned that the gantry or housing for the equipment is huge and may be frightening. Body CT scans can be produced with the patient supine or prone or lying on his or her side.

Depending on the clinical condition under investigation, contrast media may be used during CT scanning to enhance the difference in density of various structures. The view that can be illuminated by giving the patient dilute contrast material helps distinguish stomach and bowel from other soft-tissue structures and masses. Intravenous administration of water-soluble contrast material produces a temporary increase in the density of vascular structures and highly vascularized organs. This increase is referred to as enhancement and is extremely useful. For example, a great vessel and the tumor mass encasing and constricting it appear as one homogenously dense mass unless the vessel is enhanced with contrast material. As with plain film enhancement, great care must be taken to ensure that the patient is not allergic to the contrast dye material.

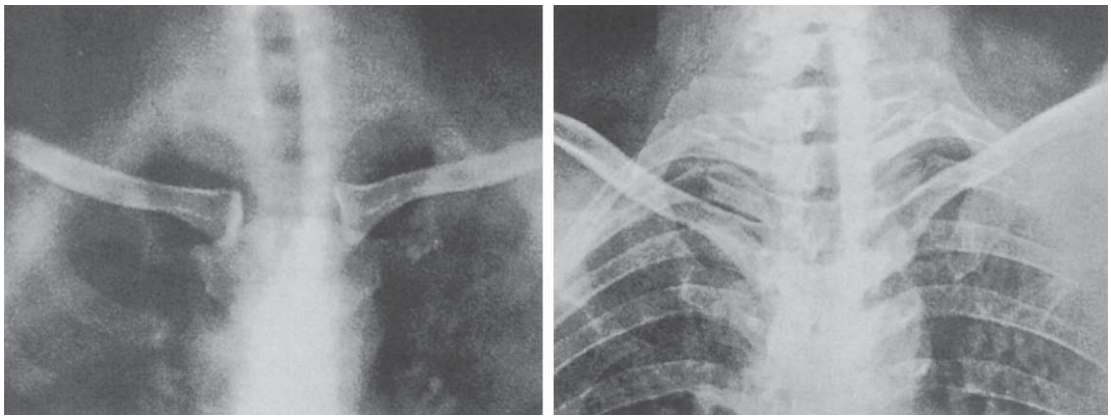

FIGURE 5-6 ■ Posteroanterior (PA) upper chest on the left and the same area of the chest with a tomogram on the right. Note the clarity of the clavicles on the tomogram. All other areas are purposely blurred out.

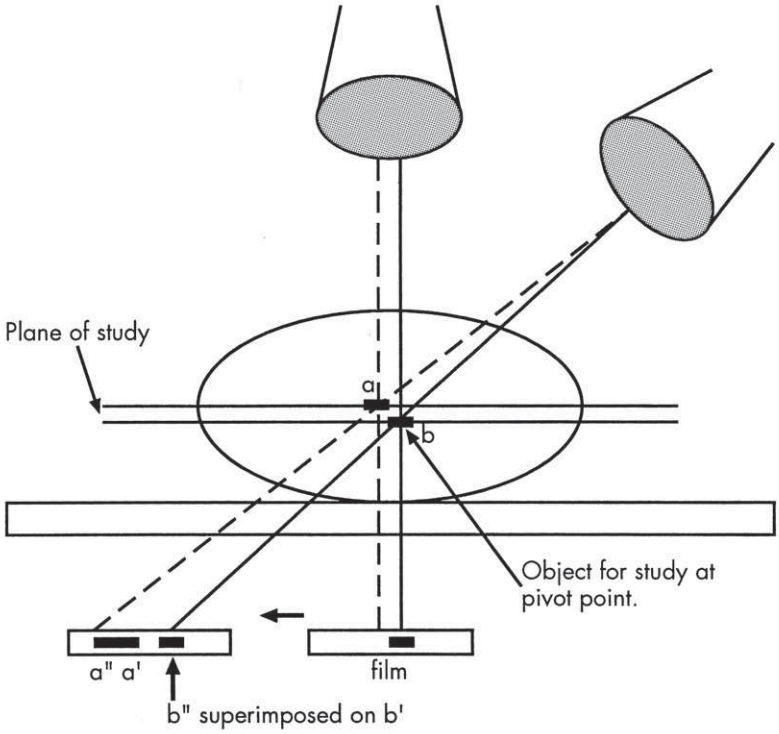

FIGURE 5-7 ■ Schematic of a tomogram, showing the movement of the film plane and the x-ray tube around the patient. The x-ray tube moves clockwise, and the film moves counterclockwise to purposely blur all area except the object for study at the pivot point.

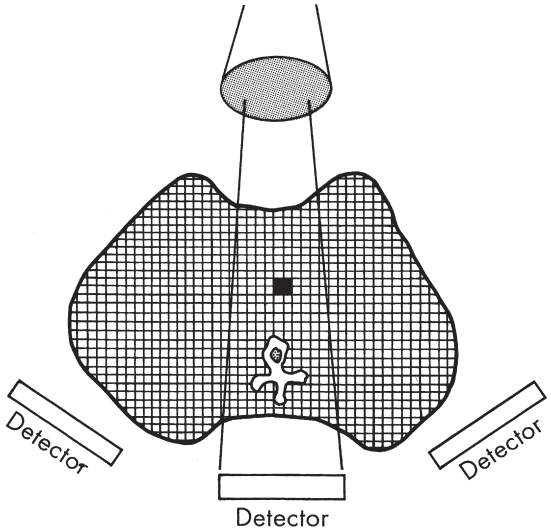

FIGURE 5-8 ■ Schematic of the CT scanner. Highlighted areas are the reference point and the detectors.

Magnetic Resonance Imaging

In magnetic resonance imaging (MRI), a patient is placed within a large cylinder that contains a superconducting magnet. Within this cylinder a second coil also surrounds the patient that consists of a radiofrequency transmitter and receiver.

The magnet causes an applied field to be exerted on the nuclei of atoms within the tissues of the body. This field causes all atomic nuclei to become aligned. Once aligned, the patient is then exposed to a specific radiofrequency set for the frequency of the hydrogen nucleus, because hydrogen is the most abundant element in tissues. The magnetically aligned hydrogen nuclei absorb this radiofrequency energy (known as the resonance frequency [RF]). Then, when the RF field is turned off, energy is shed as the protons realign themselves. This "relaxation period" gives off energy in a radiofrequency that is picked up by the receiver. Different relaxation rates (known as T2) occur because of different tissue densities. The different rates alter the received signal strength, and a computer program is used to denote gray scales.

The thickness of the sections can be chosen as well as their orientation. In addition to the transverse sections of the body, MRI can be carried out in the sagittal and coronal planes and in various desirable oblique axes.

The MRI scanner is composed of a large magnet housed in a dome-shaped machine that is hollow in the center. The patient is placed in a supine position on a sliding table that can be advanced into the hollow section of the magnet. The typical examination lasts approximately 30 minutes. While the examination is in progress, it is important for the patient to lie as still as possible. Mirrors are used for the patient to see into the room to reduce claustrophobia. Headphones can be

used to communicate with the patient. In addition, music can help reduce patient anxiety.

Positron Emission Tomography

In positron emission tomography (PET) analysis, radioactive isotopes are used that emit gamma rays from within a designated area of the body. Once the radioactive isotopes have migrated to the tissue in question, gamma rays are emitted from this tissue and are received by a set of counters set up in a ring around the patient.

The radioactive isotope that is administered to the patient has a short half-life and is bound to an appropriate chemical. Isotopes chosen for tagging are those that remain in the organ to be studied long enough to produce a usable image, but with relatively short half-lives to minimize radiation to the patient's tissues. The chemical is injected and migrates to the tissue to be studied. This process occurs because the selected chemical substance to which the isotope has been attached is involved in the physiologic metabolism of that organ. It should remain there long enough to be imaged.

An image is obtained because the radioactive isotope emits gamma rays for a brief period of time. The patient is passed through a ring of gamma-ray counters that record the gamma emissions. A few hours or days later, the isotope stops emitting detectable rays when it returns to its stable state. The return to stability is measured in terms of its half-life, that is, the period until it is seen to be emitting half as much radiation as it did initially.

PET yields an image of organ function. Such biochemical activity in vivo includes glucose metabolism, regional blood flow evaluation, heart studies, and dopamine receptor sites in the brain. The results of PET are displayed as real-time color-coded moving images. Computers can be used to process PET images to display three-dimensional images.

Isotope Scan

Technetium has proved to be the most useful radioactive tracer, and it is linked to various physiologic substances that seek different organs. This substance is deposited temporarily in bone and is called a "bone-seeker." The image obtained shows areas of more or less intensity of radiation related to the portion of the bone having increased turnover. "Hot spots" showing markedly increased activity of bone are thus seen as dense black areas on a gamma camera or rectilinear scan of the whole skeleton (Figures 5-9 and 5-10).

Unfortunately, this scan is very nonspecific and does not tell us the cause of the increased bone turn-

FIGURE 5-9 ■ Technetium bone scan. This is a radioactive tracer that can show "hot spots," which are usually indicators of metastases. The bone scan here is normal.

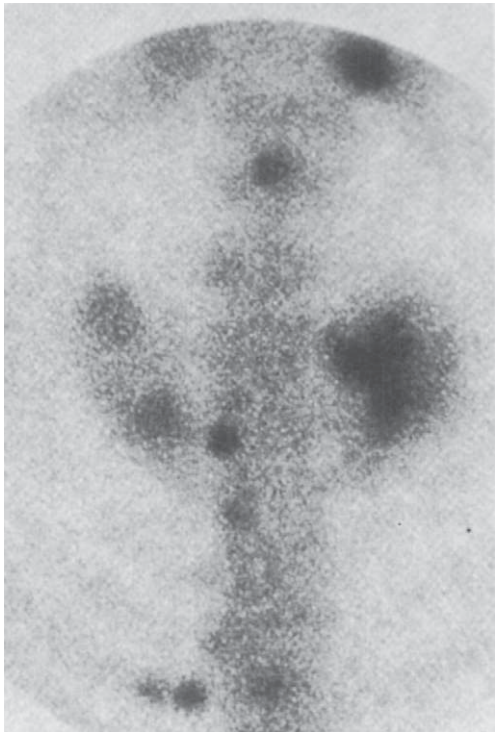

FIGURE 5-10 ■ Technetium bone scan. Dark spots on the scan show areas of uptake subsequently diagnosed as metastases.

over. If located in symmetric joint areas, for example, the increased bone turnover may be caused by acute inflammation secondary to arthritis. If located eccentrically, these spots may indicate the location of the bone metastases from the patient's known or suspected cancer. This scan is not definitive, therefore, but can be helpful with physical findings to aid in diagnosis.

Technetium may also be linked to a sulfur colloid that is normally picked up by the liver and remains there long enough to be imaged as a densely homogeneous, liver-shaped area of activity on the isotope scan of the abdomen. With any such radioactive pharmaceutical used, areas on the scan may exist where "cold spots" indicate physiologic uptake. These areas also are nonspecific in that they indicate only an area of less metabolic turnover. A large solitary cold spot in an otherwise homogeneously imaged liver thus might indicate the location of a large tumor metastasis or a benign cyst. An ordinary radiograph of a patient's abdomen might show his liver to be enlarged but would not differentiate the tumor-mass areas from the normal, metabolically active liver tissue around them. Isotope scans, like all other radiological images, must always be interpreted in tandem with clinical information about the patient.

In the typical isotope scan, the image obtained is produced by gamma radiation from the entire thickness of the organ, not from the single slice as in CT, MRI, and sonography. Like fluoroscopy, plain radiography consists of continuous or intermittent observation of tissues penetrated by x-rays. This produces dynamic radiographic information. The motion of the fetal heart is routinely monitored by "real-time" sonography and is evidence that a quiet fetus is in fact alive. Dynamic studies using rapidly sequenced CT scans during the intravenous injection of contrast material produce time-lapse information about the vascularity of a liver mass. Similarly, sequential isotope scans are used to document flow patterns such as blood flow through the heart chambers in a patient suspected of having a congenital heart anomaly.

Ultrasonography

In sonography sound waves are sent into the body and the received echo waves are processed into images. By directing these narrow beams of high-energy sound waves and then recording the manner in which the sound is reflected from organs and internal structures, ultrasonography yields an image of a slice of the body. Ultrasound does not produce an image that is as sharp and clear as CT, but it has four singular advantages: it does not produce ionizing radiation and thus produces no biological injury; it can be used at any orientation required by the anatomic region being investigated; it is far less expensive than CT or MRI; and, it can be performed at the bedside of very sick patients.

The ultrasound probe both transmits and receives echoes. The sound produced is above human hearing (20-20,000 Hz). Typical frequencies produced for diagnostic medical purposes are between 2 and 10 MHz (million hertz). Higher frequencies will produce better detail resolution but less depth penetration. For ophthalmic scanning, as in the technique of biomicroscopic ultrasonography, only a few centimeters of penetration are required; therefore, higher frequencies (7 to 10 MHz) can be used to provide optimal structural detail.

Various types of diagnostic ultrasonography are available, including A-mode, B-mode, duplex Doppler, and color Doppler imaging (CDI).

A-mode, or amplitude mode, is a single point of sound that has only one dimension. The echoes are received and interpreted as spikes on the imaging screen. Each spike, displayed on an oscilloscope screen, represents a different tissue and the distance between spikes yields significant data concerning the separation in depth of internal tissues. The use of A-scan has been largely subjugated to eye-care, where it is used primarily to measure the orbital structures and the axial length.

B-mode, or brightness mode, is the most common form of diagnostic ultrasonography in use today. This two-dimensional form of image production is used for evaluating anatomic structures within the body (Figure 5-11). A computer allows the formation of two-dimensional gray-scale images depending on signal strength. Strong reflections are displayed as white (on a black background), and progressively weaker appear as gradually darker shades of gray (Figure 5-12). Clear fluid, such as the vitreous body and aqueous, contains no reflective particles, and therefore is displayed as black. Rapid updating of a succession of two-dimensional images results in dynamic real-time moving images of structures in motion. In this way, B-mode can be used to visualize the fetal heart motion.

Duplex Doppler imaging combines two-dimensional imaging with Doppler ultrasonography for the evaluation of blood flow. The Doppler effect causes frequency changes between various moving structures. Using the two-dimensional image to identify the location of a vessel, a cursor called a range gate is positioned to provide blood flow information from a selected vessel segment. In a duplex scanner, a transducer probe contains both a transmitter and a receiver. The probe is directed at an artery and a measurement of the blood flow velocity is obtained. Doppler information can be in the form of an audible signal or can be visually displayed

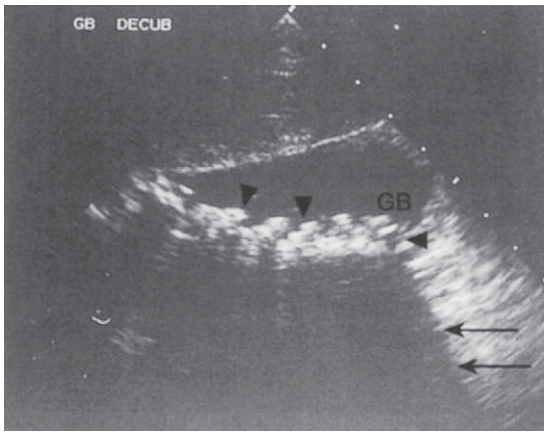

FIGURE 5-11 ■ Conventional long-axis B-mode ultrasound image of multiple gallstones *(arrowheads)* within the bile-filled gallbladder (GB). Note the acoustic shadow cast by the sound-attenuating stones *(arrows)*.

on the monitor through a special trace, allowing quantification of flow. In part because of the small size of the blood vessels supplying the eye, duplex Doppler ultrasonography has limited applications in ophthalmic scanning.

In CDI, nonmobile structures are depicted in gray scale, and moving structures, such as blood flow, are imaged in color. The operator selects colors to depict movement toward the transducer (usually red) and away from the transducer (usually blue). CDI allows rapid assessment of the presence and direction of flowing blood. The most common applications for CDI technology includes echocardiography (ultrasonography of the heart), peripheral vascular (blood flow of the limbs), and cerebrovascular (blood flow to the brain). CDI can also demonstrate blood flow in the small vessel supplying the eye, including the central retinal artery and vein located within the optic nerve (Figure 5-13). Suspected occlusion of these vessels can thus be confirmed with CDI. In addition, the technique is useful in differentiating a retinal detachment from an intraocular tumor, especially if intraocular bleeding obscures the view (Figure 5-14).

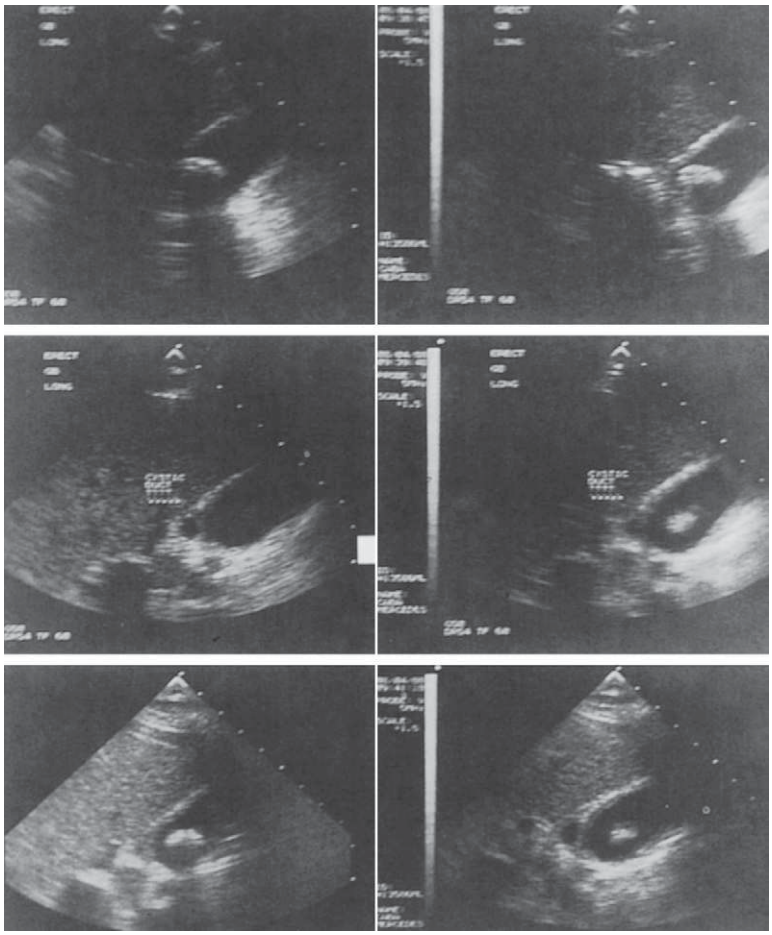

FIGURE 5-12 ■ Ultrasound, a nonionizing source, viewing the gallbladder, with no harmful biologic effects. Large dense white objects noted in each field represent gallstones.

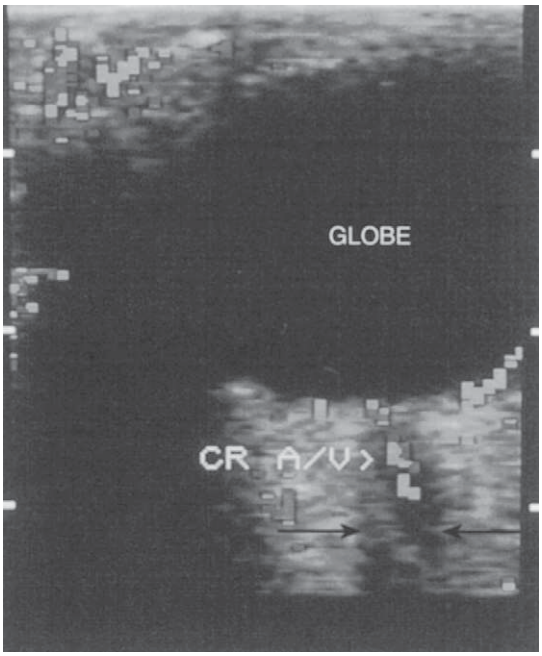

FIGURE 5-13 ■ Transverse color Doppler image demonstrating the normal central retinal (CR) artery and vein located within the hypoechoic optic nerves *(arrows)*. Blood flow is also visualized at the back of the eye corresponding to flow in retinal and choroidal vessels. Red and blue indicate flow toward and away from the transducer, respectively.

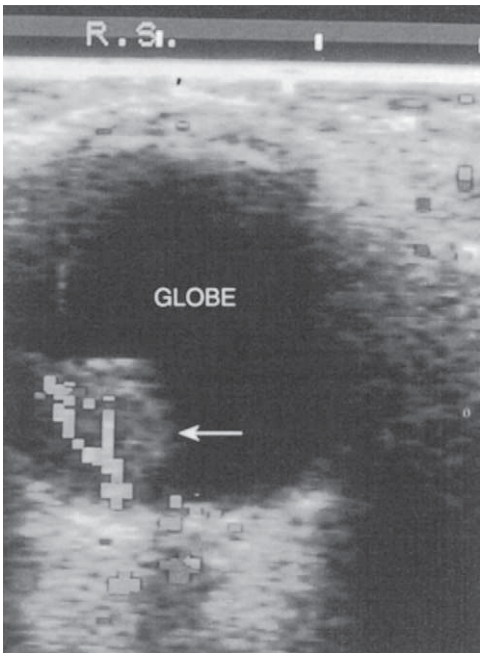

FIGURE 5-14 ■ Transverse color Doppler image of the eye in a patient with choroidal malignant melanoma *(arrow)*. Blood flow is detected from vessels in the tumor.

ORIENTING THE IMAGE

A light box, or view box, is used to backlight an x-ray image. Images should always be oriented so that it appears that the patient is facing the viewer. "Position" is used to specify the part of the body closest to the film.

Three anatomic planes are imaged in plain films, ultrasound, CT, and MRI: the axial, sagittal, and coronal planes (Figure 5-15). The axial projection is exposed with the top of the patient's head closest to the film cassette, and the beam emitted from the throat to the crest of the skull. The lower border of the image thus is occipital (dorsal) and the upper border is nasal (ventral). The left margin visualizes the right side of the body, and the right margin visualizes the left side of the body. The coronal projection, also known as posterior-anterior (PA or AP) projection, is exposed with either the chest (PA projection; Figures 5-16 and 5-17) or the back (AP projection; Figures 5-18 and 5-19) closest to the film cassette, and the beam emitted from opposite the film plane. A PA image of the skull is taken with the nose closest to the film cassette, and an AP image of the skull is taken with the back of the head closest to the film cassette. The resultant image is positioned so that the upper border is cranial and the lower border is caudal. Laterally, the image is positioned as if the patient is facing the examiner.

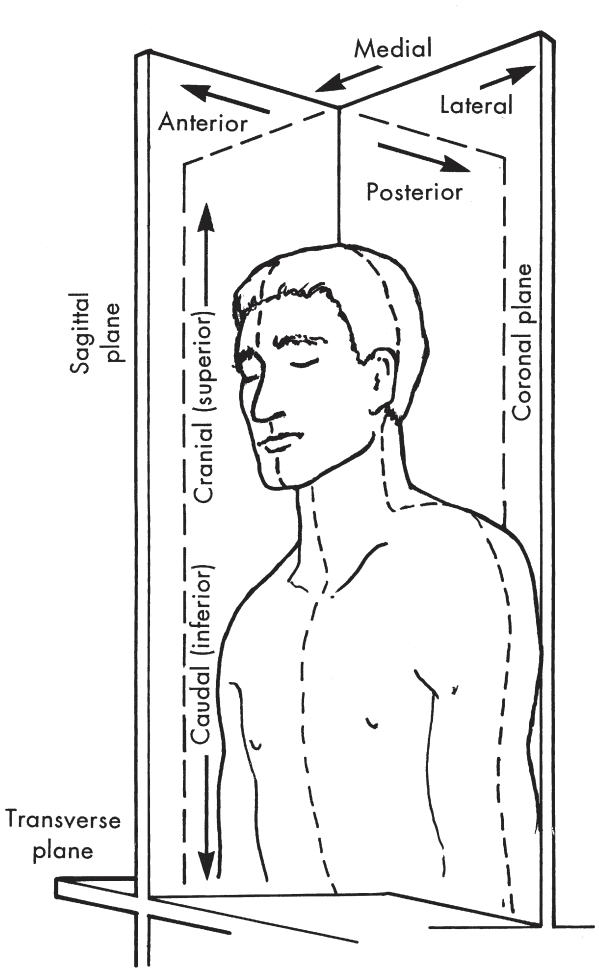

FIGURE 5-15 ■ Planes of the body.

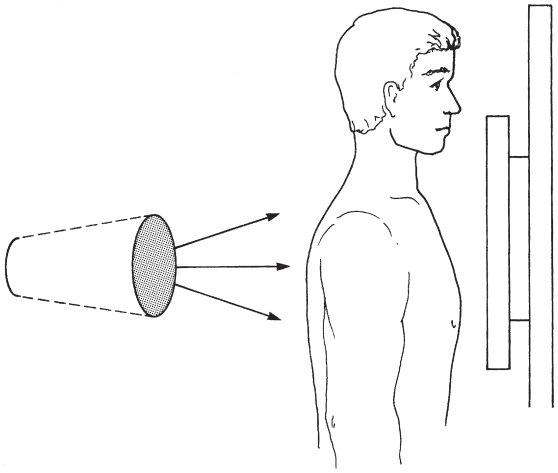

FIGURE 5-16 ■ Schematic of PA chest, showing the physical set-up with the x-ray tube behind the patient and the film plate in front of the patient.

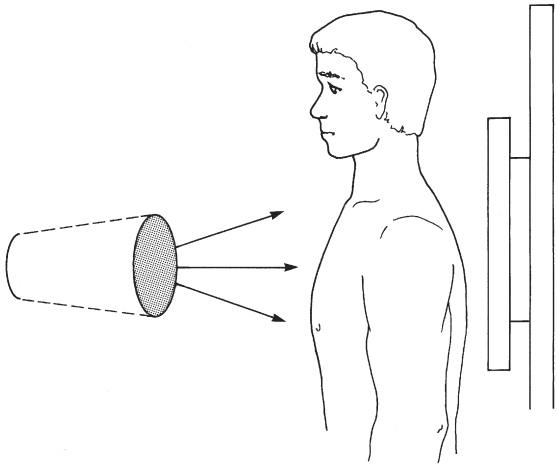

FIGURE 5-18 ■ Schematic of the anteroposterior (AP) chest radiograph showing the physical set-up with the x-ray tube in front of the patient and the film behind the patient.

The sagittal projection is exposed by positioning one side of the patient's body (Figures 5-20 and 5-21) or head closest to the film cassette and the beam emitted from opposite the film plane. This technique produces a cross-section of the eye from the cornea to the optic nerve with the resultant image positioned so that the upper border is cranial, the lower border is caudal, the right border is dorsal, and the left border is ventral.

Skull Films

Bony structures are best visualized when they are closest to the film cassette. The best image of the orbits is therefore achieved with a PA, or coronal, view (with the face of the patient nearest the film) (Figure 5-22), and the sharpest image of the occipital bone is achieved with an AP view (with the back of the patient's head nearest the film).

Skull films invariable demonstrate dark gray suture lines. Skull and orbital fractures appear darker than sutures.

Computed Tomography Scan

The CT scan is normally viewed as though one were looking up at it from the patient's feet. The CT scan should be held so that the patient's left side is presented as if the patient is facing the examiner. After the scan is performed, permanent images are produced by photographing the monitor screen with a camera. The CT scan slices in sequence so that one slice can be linked to another. The slices above and

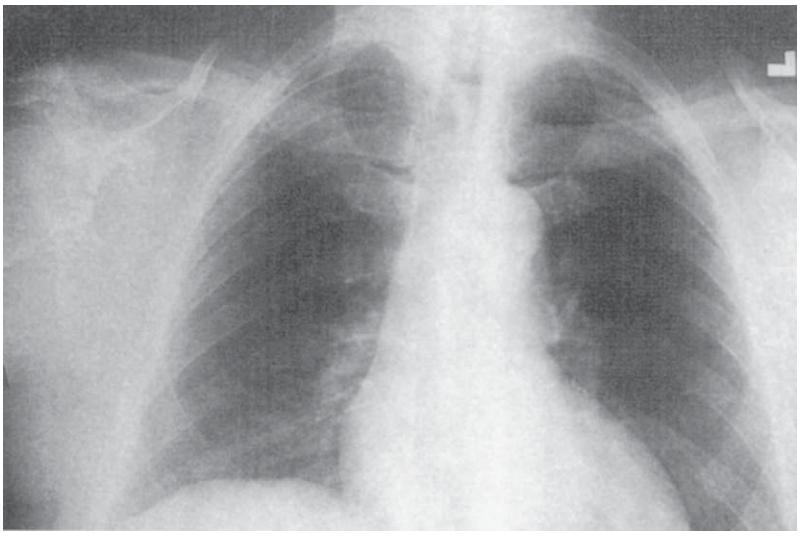

FIGURE 5-17 ■ PA chest radiograph. Note the clarity of the clavicles and the anterior ribs.

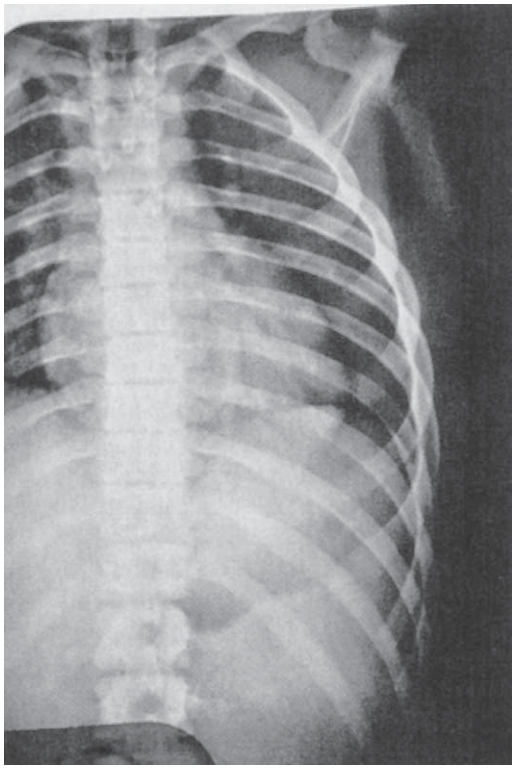

FIGURE 5-19 ■ AP chest radiograph. Note that the spinal column actually restricts the normal view of the chest. The AP view is usually used when the patient is not ambulatory and the portable x-ray machine is needed for the bedside.

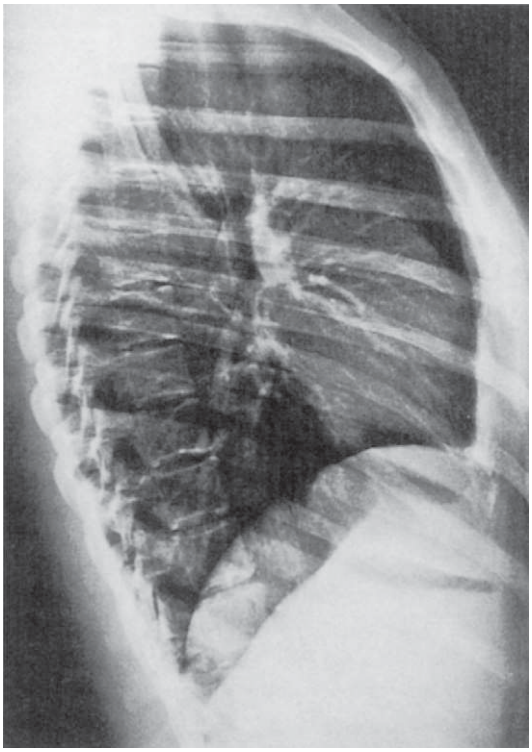

FIGURE 5-20 ■ Lateral view of the chest.

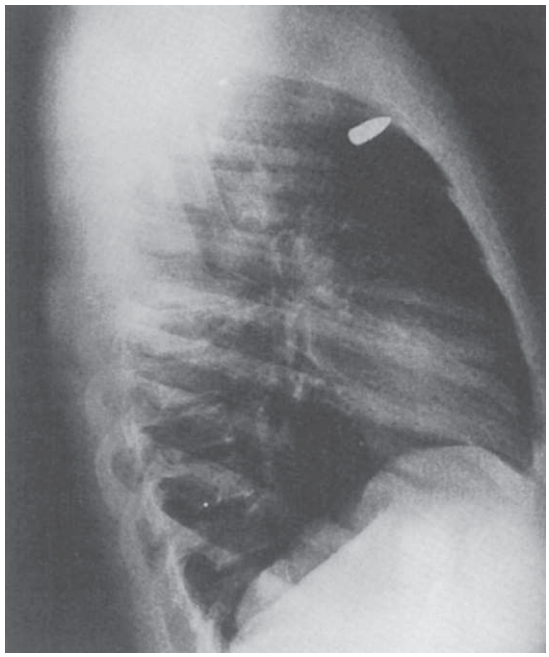

FIGURE 5-21 ■ Lateral view of the chest, cross-section showing the anterior level of the chest with a metallic foreign body.

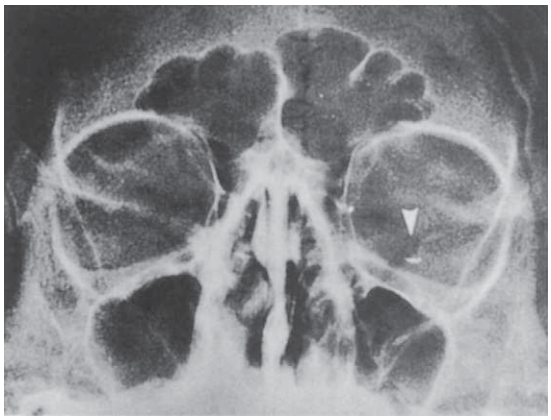

FIGURE 5-22 ■ Coronal (Caldwell's) view of both orbits showing the sphenoid wings and ridge, and part of the orbital floor. Note the presence of a metallic foreign body in the left orbit which is easily visualized on plain films.

below give additional information about the structure of an organ (Figure 5-23).

The usual CT series of scans consists of contiguous 10-mm-thick slices through the region requested (Figure 5-24), but slices as thin as 1.5 mm can be obtained when finer detail is needed for diagnosis. In ordering orbital scans, the slices are usually 2-mm-thick cuts through the tissue in question (Figure 5-25). The x-ray dose per slice varies from 1 to 4 rad (but only to the slice being imaged) and is comparable to the exposure for conventional radiographic studies of the area. (Rads are units of radiation.)

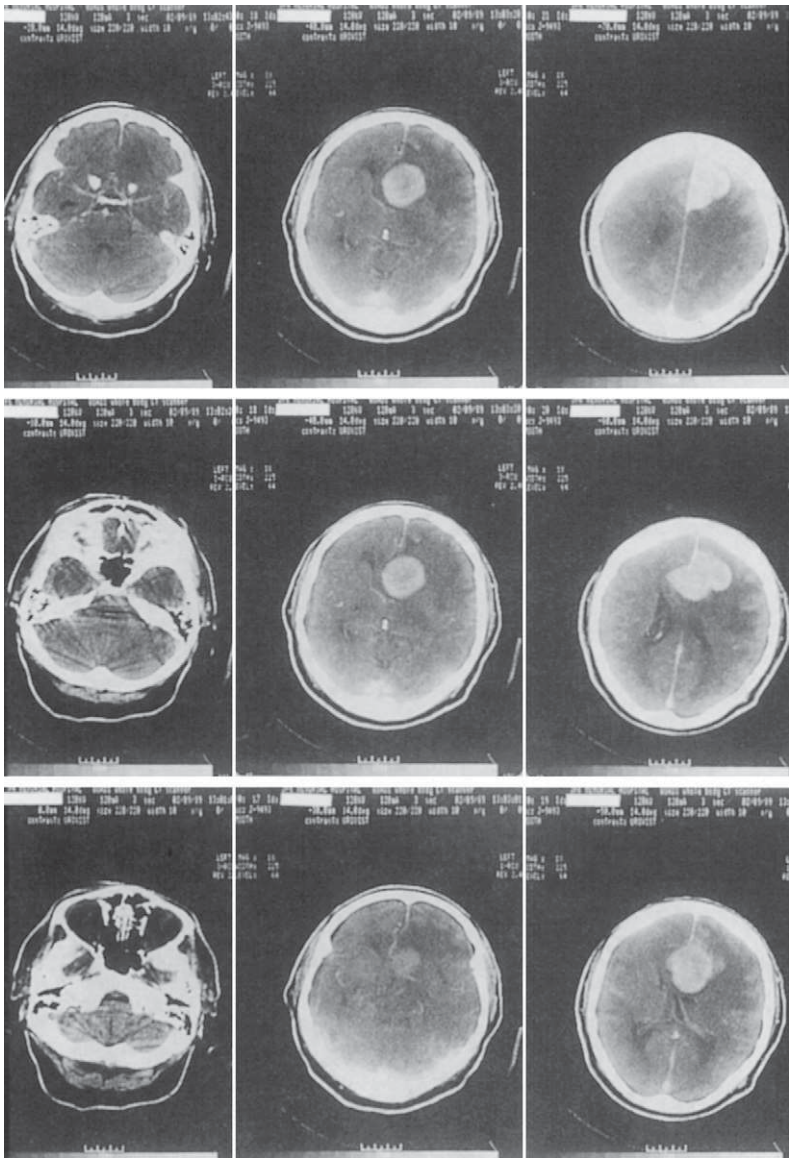

FIGURE 5-23 ■ CT scan of a large tumor located in the cerebrum. Note that slices above and below the lesion provide an evaluation of the structures adjacent to the tumor.

The image is degraded by the presence of high-density metallic materials used for joint prosthesis, and by motion initiated by the patient or by internal organs. CT scanners require only 1 to 10 seconds to complete a slice, and a patient must hold his or her breath to prevent motion artifacts on the image.

RADIOLOGY OF THE EYE AND ORBIT

Four basic methods exist to image the eye and orbital structures: plain films, computed tomography, MRI, and orbital ultrasonography. An orbital scan can be ordered through the local hospital radiology department. On a blank prescription pad or radiology form available from the local hospital radiology department, the clinician should write the patient's name, age, and diagnosis clearly. A tentative diagnosis is adequate, and the type of scan desired should be indicated. If any questions arise, the radiologist will contact the ordering physician.

Plain Films of the Eye and Orbit

A radiological work-up for a patient with orbital disease or ocular disease involves specific helpful views. These views include Caldwell's position, Waters' positions, lateral view, basilar view, and optic canals view.

Caldwell's position is a coronal section that allows one to view both orbits, the sphenoid wings and ridge, and part of the orbital floor (Figure 5-26).

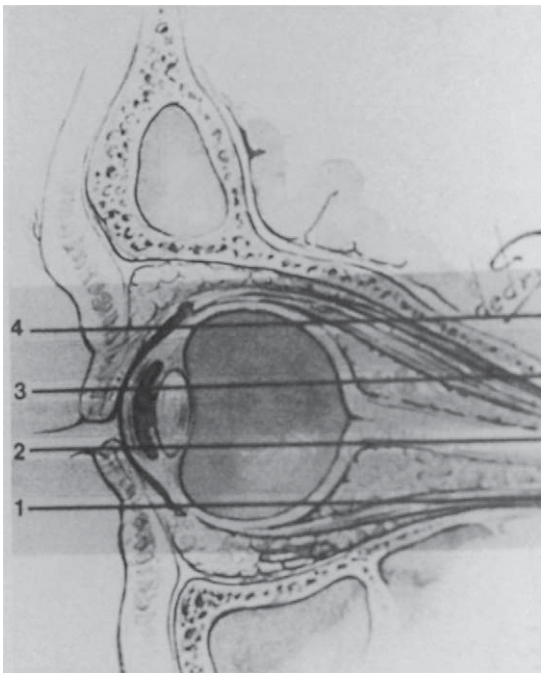

FIGURE 5-24 ■ Level four CT of orbits. This schematic shows approximately where the cuts are made. The cuts do not overlap.

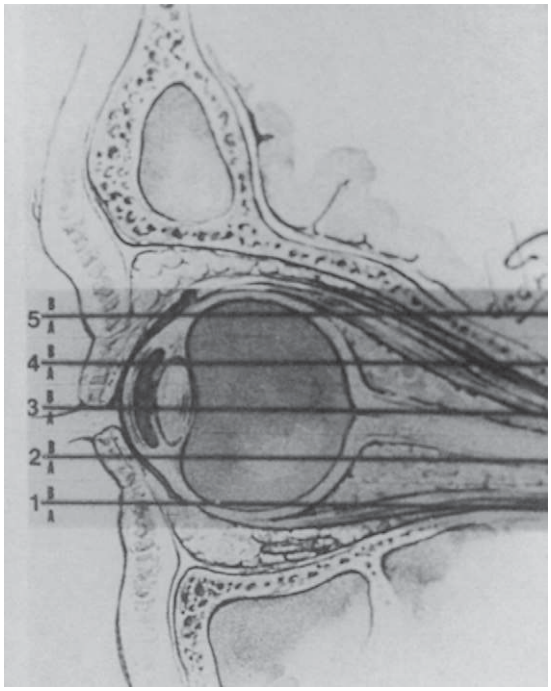

FIGURE 5-25. ■ Level five CT of the orbits. This schematic shows approximately where the cuts are made. The cuts are overlapping.

Waters' position is a transverse section that allows a view of the paranasal sinuses and floor and roof of the orbits and the maxillary antrum (Figure 5-27). The Waters' position scan is used frequently by otolaryngologists and allergists. The ophthalmic application is limited to cases of suspected orbital floor fractures in trauma.

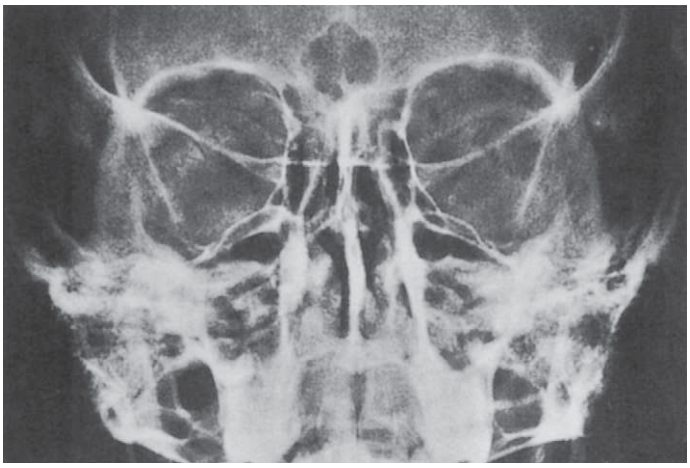

FIGURE 5-26 ■ Caldwell's position, which is the same as a coronal, or PA, view.

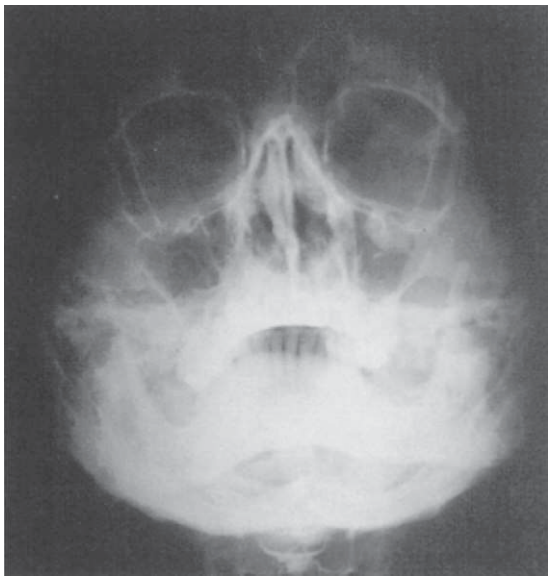

FIGURE 5-27 ■ Waters' view, a transverse scan. This scan allows the paranasal sinuses and the roof and floor of the orbits to be viewed.

The lateral view is a cross-sectional view taken from the side (Figure 5-28). This view should enhance subtle pathologic changes so that the depth of level of the lesion is indicated. For example, the lateral view of the sella turcica, as seen in Figure 5-29, shows the sella and anterior clinoids so the examiner can detect problems like empty sella syndrome and pituitary disease.

Scans of the optic canals are magnified views that can demonstrate the foramen in the skull (Figure 5-30).

The basilar view is a transverse scan that allows the posterior wall of the orbit, the maxillary sinus and the optic canals, to be visualized (Figure 5-31).

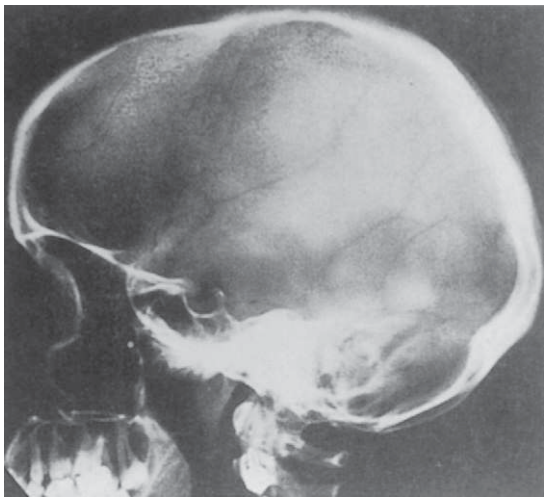

FIGURE 5-28 ■ Lateral view, which is the same as a sagittal view.

Visualization of vascular structures of the eye may still require intravenous contrast media. Arteriography is used to selectively show the vascular tree within an organ (Figure 5-32). The radiopaque dye is injected into an artery, and subsequent arteries are viewed according to the study in question. This method is particularly helpful in the study of malignancies, because they are usually highly vascular in nature. Arteriography is also helpful in diagnosing aneurysms. This method does, however, have a higher morbidity rate than CT, therefore it is used with caution and only when necessary, not as a routine test.

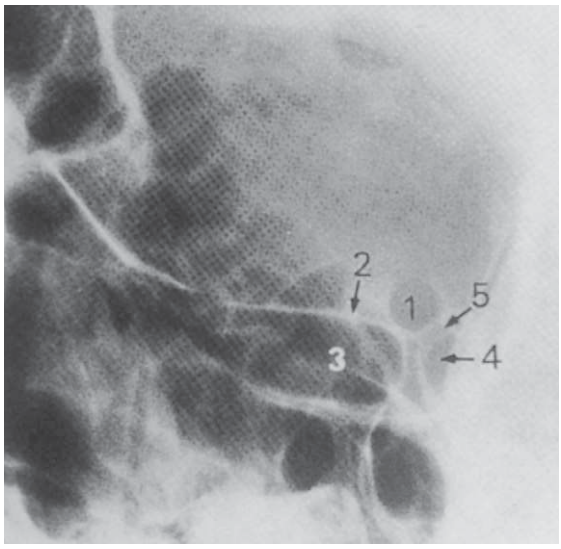

FIGURE 5-30 ■ Optic canal scan. This scan gives an enlarged view of a very specific area within the orbit. This view can detail the foramen in the skull.

Computed Tomography of the Eye and Orbit

Axial images of the eye and orbit parallel to orbital axis, the optic canal, and the chiasm visualize the optic nerve and the horizontal recti muscles along their entire path. The axial image is best used to visualize the entire anterior visual pathway. Data taken in the axial plane may be reformatted to yield images in the coronal, sagittal, and oblique parasagittal planes. This

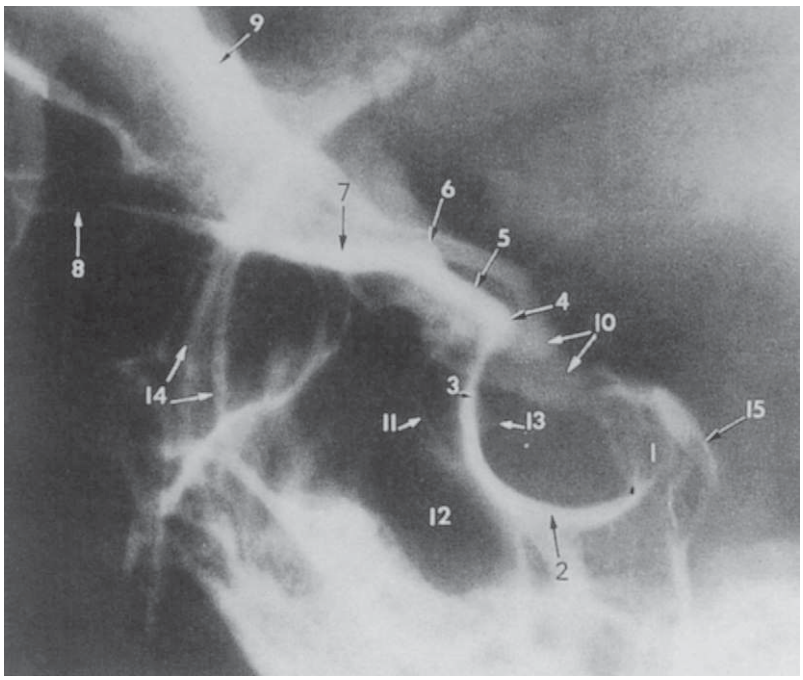

FIGURE 5-29 ■ Lateral, or sagittal, view of the sella turcica, showing sella and anterior clinoids.

reformation minimizes radiation exposure to the patient, because these additional planes of section are generated by the computer information after the patient has left the scanner. If the orbit is angled 20 degrees downward so the plane of the image is parallel to the orbital floor, better images of the oblique muscles and inferior rectus muscle are obtained.

Orbital CT scans rarely require contrast enhancement because a wide variation in tissue densities exists within the major orbital structures. High-contrast differentiation therefore occurs in CT images despite the lack of contrast media involvement. Contrast material may be necessary in cases of visual loss, possible infection, and intracranial involvement.

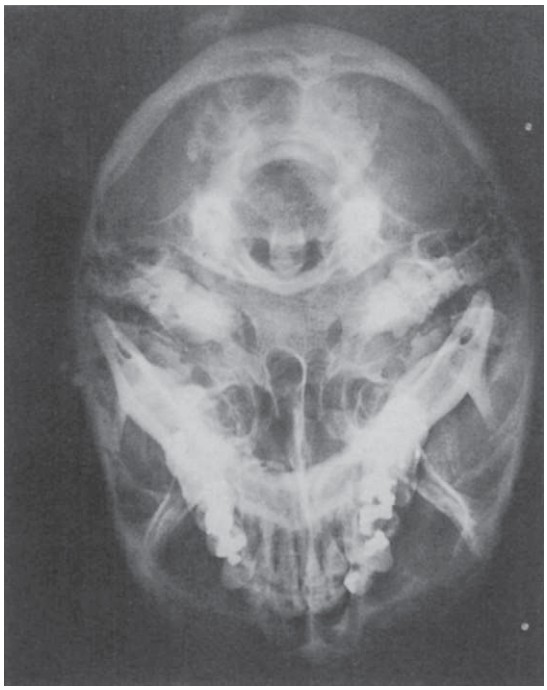

FIGURE 5-31 ■ Basilar view, a transverse scan allowing visualization of the posterior wall of the orbit, the maxillary sinus, and the optic canals.

CT can define fine anatomic detail and thus can well visualize and characterize the morphology and the site of globe, extraocular muscle, optic nerve, and orbital tissue pathology. The CT findings should be correlated with the patient's history, symptoms, clinical signs, laboratory testing, and other imaging data.

Direct coronal views are best used to evaluate the orbital roof, floor, and medial walls for signs of erosion, blowout fracture, neoplasm, and chronic infection. Axial views are typically used for almost all other evaluations of ocular conditions. One significant exception is extraocular muscle involvement in Graves' disease, which is best visualized by ordering a paraxial CT reformation perpendicular to the course of the muscles to best judge true muscle thickness.

Ocular Pathology on Computed Tomography Scans

CT can define fine anatomic detail and so can well visualize and characterize the morphology and site of globe, muscle, optic nerve, and orbital tissue pathology. The CT findings should be correlated with the patient's history, symptoms, clinical signs, laboratory testing, and other imaging data.

Axial sections are typically 1.5 mm thick to maximize detail. The most desirable plane to use is parallel to the optic nerve. Data taken in the axial plane may be reformatted to yield images in the coronal, sagittal, and oblique parasagittal planes. This reformation minimizes radiation exposure to the patient,

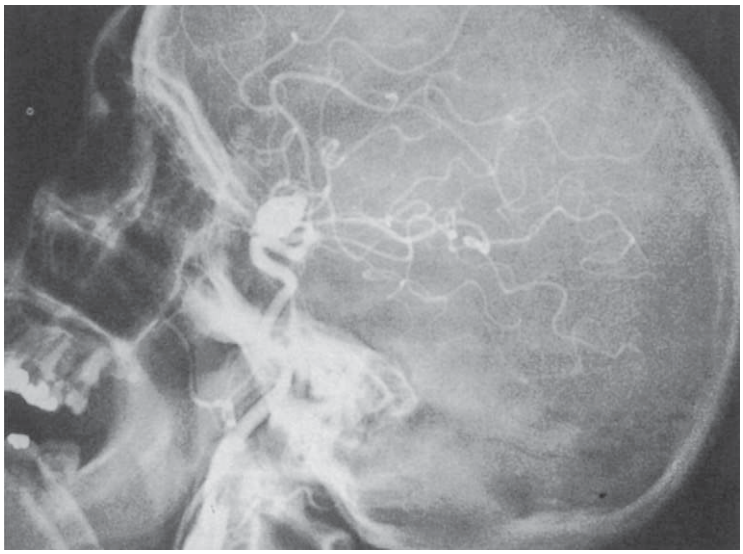

FIGURE 5-32 ■ Cerebral angiography. This scan shows the vascular tree on a lateral, or sagittal, view. A large internal carotid aneurysm is present.

because these additional planes of section are generated by the computer information after the patient has left the scanner.

Contrast material is necessary in cases of visual loss, possible infection, and intracranial involvement.

CT has limited use in eye care because most ocular pathology can be diagnosed from standard examination techniques. In selected cases, however, CT can be invaluable. In situations in which cornea, lenticular, or vitreous opacity prevents ophthalmoscopic evaluation, CT is of great benefit. For example, in children with leukocoria CT is used to detect an underlying retinoblastoma. CT can also be used to detect the extraocular or intracranial extension of an intraocular mass.

In addition to tumors such as uveal melanoma, CT can be of diagnostic value in cases of Graves' disease, retinal detachment, severe uveitis lens subluxation, disc abnormalities, optic nerve pathology, and vascular and inflammatory lesions.

Magnetic Resonance Imaging of the Eye and Orbit

Three types of MR images can be ordered to analyze ocular structures. The T1-weighted (T1W) images cause a bright signal intensity seen in orbital fat, intermediate intensity seen in optic nerve and extraocular muscles, and low intensity seen in the vitreous. T1W images demonstrate good anatomic detail because the orbital fat is so bright, but are poor in differentiating bright structures, such as the orbital fat, from adjacent intermediate intensity structures, such as the lacrimal gland. Structures that impart a low signal intensity, such as the layers of the eye, the vitreous, lens, and ciliary body, are poorly differentiated in T1W images. The overwhelmingly bright images of the orbital fat produced by a T1W image can be suppressed in various ways. Fat-suppressed images allow for better delineation of the posterior globe and optic nerve.

A T2-weighted (T2W) image produces a bright signal in fluids, and thus demonstrates well the vitreous and cerebral spinal fluid. Fat signals are darker in T2W images than in T1W images. T2W images suffer from lower quality images than T1W images because of patient movement during longer scan times.

Diagnostic medical imaging using MRI is an excellent tool to help discriminate normal ocular anatomy from pathologic states in both the eye and orbit. Ocular pathologies detectable in MR images include, among others, retinal detachment and ocular tumors.

Retinal detachment (RD), a separation of the sensory retina from the underlying retinal pigment epithelium (RPE) causes an accumulation of fluid within the potential subretinal space. Retinal detachments may be induced by a retinal tear (a rhegmatogenous RD) or by a mass, inflammatory, or fibroproliferative source (nonrhegmatogenous, or exudative, RD). An RD can be visualized on an axial MRI as a "V"-shaped structure with its apex towards the optic disc and its base facing the ciliary body. On coronal MRI, the RD appears as a folded membrane within the vitreous cavity.

The most common tumor to involve the uveal tract is malignant melanoma. Because of the paramagnetic properties of melanin, which contains stable radicals, malignant melanoma appears on T1W images as high-intensity, solid mass areas (Figure 5-33). On T2W images, malignant melanomas appear as less intense than the vitreous signal. An associated RD caused by exudation appears as a hyperintense, folded membrane on T1W images similar to the intensity of the melanoma. On T2W images, however, the melanoma appears hypointense, and both the vitreous cavity and the RD appear hyperintense.

Orbital pathologies detectable on MR scans include, among others, tumors of the optic nerve, blood vessels, and lacrimal gland; thyroid ophthalmopathy; and orbital trauma. MRI is an excellent way to evaluate optic nerve gliomas and possible posterior extension of this tumor along the visual pathway. Abnormal blood vessel growth within the orbit, such as the capillary hemangioma, is well documented by MR scan techniques, which demonstrate a vascular, heterogeneous mass, with an intensity greater than extraocular muscle and less than fat. MR scans can differentiate lacrimal gland tumors and inflammation from the surrounding orbital fat.

The clinical finding of proptosis should instigate an investigation into the possibility of thyroid ophthalmopathy (Graves' disease), because it is the most common cause of unilateral and bilateral exophthalmos. An infiltrative ophthalmopathy with enlargement of the extraocular muscles may cause proptosis, diplopia, corneal desiccation, and optic nerve compression. MR scans in these cases may reveal extraocular muscle enlargement and the relationship of these muscles to the optic nerve at the orbital apex. Changes in the orbital bones caused by thyroid ophthalmopathy are better depicted by CT images, and are important if bone decompression surgery is contemplated.

MRI is contraindicated in cases of possible metallic intraocular foreign body, because the magnetic field may cause movement of the metal particle. In cases of trauma, the most frequent orbital fracture involves the floor or medial wall, the weakest portion of the bony orbit. These blow-out fractures are best demonstrated on CT scans. Herniation of fat and distortion of muscle, however, is shown better with MRI than CT.

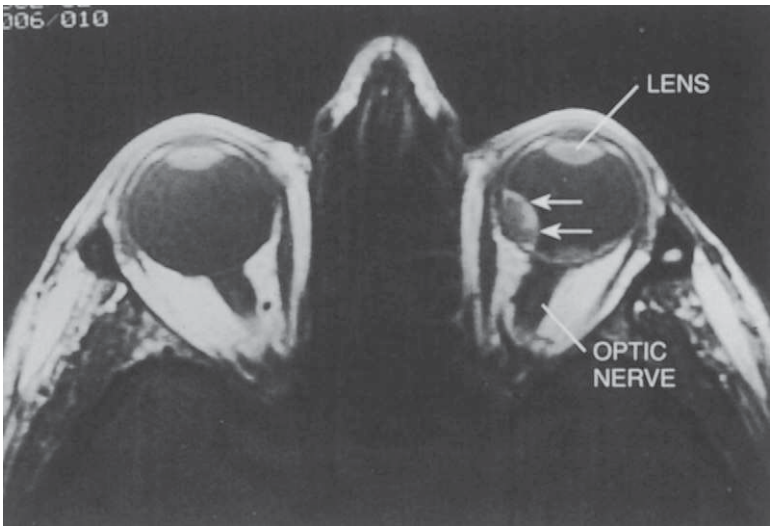

FIGURE 5-33 ■ Axial T1W magnetic resonance image of a patient with choroidal malignant melanoma of the left eye *(arrows)*. MR images allow simultaneous evaluation of both orbits. Orientation on an MR image is placed as though the examiner were looking up from the feet of the patient, so that the image of the left eye is placed on the right-hand side when looking at the film.

Ultrasonography of the Eye and Orbit

The initial imaging procedure of choice in cases of ocular pathology is often orbital sonography. This method is popular because it is a relatively inexpensive, noninvasive, nonradiating, and low-risk modality. It is most useful in the detection of intraocular foreign bodies and the evaluation of lens, vitreous, and retinal pathology. One weakness of orbital ultrasound is that it is highly dependent on the competence and experience of the sonographer.

Sonography is based on sound propagation, the reflection of those sound waves from structures, and the interpretation of the retrieved echoes from those reflections. The higher the frequency of the sound wave, the better the resolution. These high-frequency waves also have poorer tissue penetrance when compared with lower frequency sound waves. In ocular ultrasonography a compromise is reached between maximum penetrance and optimal resolution.

The echoes may be displayed in two ways: amplitude modulation (A-mode) and brightness modulation (B-mode). The A-mode displays echoes as spikes that represent the location and size of intraocular structures. The A-mode is often used in the presurgical work-up for cataract extraction to determine the axial length when the power of an intraocular lens is calculated.

The B-mode represents two-dimensional anatomic images of a cross-section of the eye. In B-mode, the brightness of the echo represents the reflectivity of the structure. Normal orbital fat has the highest reflectivity and produces very bright images. Slightly less bright is the infiltration produced by thyroid ophthalmopathy at the muscle cone, a neurofibroma, a lacrimal gland tumor, and a cavernous hemangioma. Of medium intensity are hematoma, lymphangioma, and the optic nerve glioma. Low-intensity lesions include the varix, dermoid, mucocele, and some malignant tumors. Cystic masses produce very low reflectivity signals.

In general, ocular ultrasound seems to be the best technique to evaluate intraocular lesions, because it can characterize lesions as small as 1.0 mm. In addition, ultrasound is often used before CT or MRI to examine a patient who might have an intraorbital lesion associated with exophthalmos. Ultrasound can evaluate the anterior half of the retrobulbar optic nerve and thus is effective in the evaluation of the patient with an optic nerve glioma or optic nerve sheath meningioma. Ultrasound can help delineate the structure of an intraconal, retrobulbar cavernous hemangioma on B-scan as a homogenous irregular echo with medium intensity.

In Graves' disease, the extraocular muscles are infiltrated with mucopolysaccharides and their enlargement can be measured with both B-scan and A-scan ultrasonography. In cases of thyroid ophthalmopathy, ultrasound can demonstrate extraocular muscle involvement by an increase in muscle reflectivity and blurring of the muscle margins.

DIAGNOSTIC IMPLICATIONS

The help of a radiologist should be sought when the clinician is planning the diagnostic protocol for a patient with ocular disease. CT and MRI scans should usually be considered sophisticated and costly studies that are reserved for specific disorders. Less expensive

procedures such as plain films and ultrasonography should be used for routine evaluation. Important exceptions to this guideline are patients with trauma and central nervous system emergencies. In head trauma the superior capacity of CT to recognize intracranial hemorrhage and organ rupture can speed diagnosis and often saves lives. CT much more efficiently informs managing clinicians about the order in which treatment procedures should be undertaken.

The optometrist must have a possible diagnosis to submit a patient for radiologic evaluation. The radiologist performs whatever testing is needed to rule out the suspected diagnosis, and written confirmation and test results are forwarded to the optometrist's office.

ACKNOWLEDGMENT

I wish to thank Drs. George E. White, Barry B. Goldberg, and Daniel A. Merton for contributing the chapter on Radiology in the first edition of this book.

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CHAPTER 6

Vascular Disease

CHAPTER OUTLINE

VASCULAR DISEASE RISK FACTORS

The leading cause of vascular disease is atherosclerosis, a disorder in which an abnormal plaque, known as an atheroma, develops on the inner wall of an artery. The atheroma has a deleterious effect on the blood flow through the artery. The atheroma, the initial growth of which is typically outward and away from the lumen, may partially obscure the vessel, thus leading to tissue ischemia and pain. For example, atherosclerosis of the coronary arteries may cause effort-induced chest pain, or angina.

In addition, rupture of the plaque may cause collagen from within the lesion to contact blood coagulant factors, resulting in a blood clot, or thrombus. The thrombus may completely obscure the artery and lead to a complete loss of blood flow to a region of the involved organ. A thrombus of a carotid artery, or carotid stenosis, may cause a stroke with profound loss of neurological functioning.

The atheroma may instead break apart spreading debris from the lesion downstream. These particles, known as emboli, may occlude distal arterial branches and cause tissue ischemia. Embolic debris may be visualized in the retinal arteries by ophthalmoscopy. These Hollenhorst plaques, made of calcium, fibrin, or cholesterol, most often originate from atheromatous plaques of the carotid artery, although a cardiac source should also be explored. Retinal arterial plaques may lead to central or branch retinal artery

occlusions, with subsequent retinal ischemia and possible vision loss.

Chronic atherosclerosis may produce no clinical manifestations early in the disease. Chronic undiagnosed renal failure may be the result of atherosclerosis of the renal arteries or arterioles. Atherosclerosis of the afferent and efferent arterioles of the kidneys may cause a reduced glomerular filtration rate with eventual renal failure. This condition may exist for decades with no systemic symptoms before it is ultimately diagnosed by medical investigation.

The target organs for atherosclerotic damage are obviously the heart, brain, eyes, and kidneys, but any organ system may become involved. Compounding this derangement of the arterial cell wall is systemic hypertension which acts on a chronic basis to affect these target organ arteries. Coexisting secondary factors such as abnormalities in plasma lipoproteins, diabetes, gender, race, lifestyle and genetics modify the development of atheromatous lesions.

THE VARIABLE PRESENTATION OF ATHEROSCLEROSIS

The majority of vascular disorders are caused by atherosclerosis. The leading cause of death and disability in developed countries, atherosclerosis is the root cause of most cases of stroke, gangrene, heart attack, and renal failure.

Atherosclerosis may evolve slowly during long periods of time with no observable clinical signs. Indeed, in some long-lived individuals, widespread and profound atherosclerosis never causes any detectable manifestations of the disease. In most cases, however, transient cardiac or neurological signs are expressions of chronic vascular derangement. In some rare instances, dramatic, disabling, and acutely life-threatening episodes herald the previously undetected presence of atherosclerosis. Differences in individual anatomy and physiology, genetics, and environment account for such extreme variability in the manifestation of vascular disease.

THE PATHOGENESIS OF ATHEROSCLEROSIS

Initiation of Atherosclerosis

The initial site of lesion formation in the development of atherosclerosis is located in the intima of the blood vessel. This innermost layer is composed of endothelial cells in contact with the blood. Although evidence for a source of initial injury is lacking, frictional forces exerted by the blood stream are thought to insult this intimal lining, particularly at extreme bends and bifurcations, and lead to breaks in the endothelial lining. Lipoproteins accumulate in these breaks and bind to proteoglycan molecules that increase the time the damaging lipoproteins reside within the lesion. By preventing their exit from the lesion, these proteoglycan molecules (mostly sulphate molecules) allow the lipoproteins to become chemically modified by oxidation. Oxidized lipoproteins contribute to the development of the lesion by stimulating the arterial endothelial cells to produce chemoattractant cytokines that subsequently attract monocytes to the intima. These monocytes then transform into lipid-rich foam cells within the site of the lesion and elaborate growth factors that stimulate the proliferation of smooth muscle cells. The resulting lesion is known as a "fatty streak" and has been demonstrated postmortem in young children.

Leukocyte Recruitment and Adhesion

Hypercholesterolemic states increase the serum concentration of lipoproteins. When shear forces of the blood stream damage the endothelial wall, lipoproteins accumulate in the intima and are sequestered from plasma antioxidants. This process increases the chance of lipoprotein (especially low-density lipoprotein [LDL]) oxidation within the site of the lesion and triggers an inflammatory response. The inflammatory response within the fatty streak begins with recruitment of leukocytes and their adherence to receptors on the surface of the endothelial cells. These white blood cells are mostly monocytes and lymphocytes. Oxidized LDL then promotes the chemotaxis of leukocytes into the intimal lesion. The uptake of lipoprotein molecules also allows differentiation of the monocytes into macrophages and their transformation into the foam cells. Mononuclear phagocytes remove lipoproteins from the developing lesion and help prevent lesion formation. If lipid entrance through the arterial wall surpasses clearing by lipid-loaded macrophages, however, then lipid accumulates in the lesion and an atheroma forms.

Atheroma Formation

The formation of an atheroma from a fatty streak is enhanced by the death of some lipid-laden foam cells in the center of the atherosclerotic plaque. The accumulation of dead foam cells forms the necrotic core of the atheroma. The developing atherosclerotic lesion is characterized by the proliferation of smooth-muscle cells within the expanding intima. These smooth-muscle cells are stimulated to proliferate by the elaboration of growth factors by monocytes. A fibrous cap then forms over the lipid cone.

Thrombus Formation

Almost all atheromas begin as fatty streaks, but not all fatty streaks become atheromas. The arrival of the smooth-muscle cells clearly heralds the transition of

fatty streak to atheroma. In this way the simple accumulation of lipid-rich foam cells is transformed into an advanced atheromatous lesion characterized by fibrous tissue. The smooth-muscle cells are invested with a collagen-rich and elastin-rich extracellular matrix and are located in the tunica media. Microthrombi form at these sites and are rich in platelets. In addition, microvessels form around the atheroma and deliver still more leukocytes to the lesion. These microvessels may hemorrhage and lead to microthrombosis within the lesion. Ultimate thrombosis of the plaque occurs because of physical disruption of the fibrous cap.

Thrombus Healing

When the disrupted fibrous cap heals, fibrosis of the cap can occur. This fibrosis, in turn, leads to narrowing of the arterial lumen. When healing ensues, smooth-muscle cells proliferate within the lesion that further narrows the lumen. If the luminal size decreases to the point of near occlusion, collateral vessel growth may be stimulated and prevent any target organ symptoms. A sudden rupture of the plaque with subsequent arterial occlusion, however, may lead to profound target organ destruction, as occurs in myocardial infarction.

Flow-Limiting Stenosis

This narrowing of the arterial lumen occurs late in the history of atheroma development, because the growth of the early plaque is outward and away from the intima. If rupture of the fibrous cap with thrombosis does not occur, the atheroma will begin to narrow the lumen once the plaque reaches a significant size. This process results in stable and chronic conditions to the target organs. The chest pain experienced by patients with demand-induced angina pectoris is caused by long-term, low-grade heart muscle ischemia secondary to coronary artery stenosis. The risk of rupture increases in atheromas with thin fibrous caps, high content of macrophages and a concentrated lipid core. Plaques with thick caps and a low concentration of core lipids are at a reduced risk of rupture.

Antithrombolytic Mechanisms

The normal artery wall has several fibrinolytic mechanisms that resist thrombus formation and lead to clot lysis. Molecules that act as antithrombolytic agents include urokinase-type plasminogen activators, heparin sulfate proteoglycans, prostacyclin, and thrombomodulin. Nitric oxide is a molecule that is produced by the arterial endothelium and, at low concentrations, acts as an antiinflammatory and a vasodilator. In addition, cholesterol molecules are continually removed from the atheroma by high-density lipoproteins (HDL). Ultimately, several complex and competing mechanisms contribute to the formation or prevention of the atheroma.

Risk Factors

The most significant and best understood risk factor in the formation of atherosclerosis is the presence of high levels of blood lipids. In addition, diabetes mellitus accelerates the formation of atheromatous plaques by causing the diabetes-associated dyslipidemia. Hyperglycemia acts similarly to oxidation to modify LDL molecules to potentiate atherogenesis. Hypertension accelerates the formation of atherosclerosis and, left untreated, may shorten the patient's lifespan by much as 20 years because of stroke, renal damage, or congestive heart failure. The profile of a patient who is at greatest risk is an insulin-resistant, type II diabetic with hypertension, hyperlipidemia, low HDL, and central fat retention. Nonlipid atherogenesis risk factors include elevated homocysteine levels and tobacco use, both of which potentiate thrombosis by as yet unknown mechanisms. Gender plays a significant role in atherogenesis, with males at greater risk of atherosclerosis than premenopausal women. It is believed that hormone levels in the premenopausal woman, particularly estrogen, have a vasoprotective effect on the vessel wall. The postmenopausal female patient will be at greater risk for atheroma development.

TARGET ORGAN DAMAGE IN ATHEROSCLEROSIS

Effects on the Heart

Flow-limiting stenosis results in stable coronary conditions such as demand-induced angina pectoris. Occlusion of the atheroma in the coronary artery may lead to acute myocardial infarction. In some cases, a slowly developing coronary atheroma causes low-grade hypoxia of the heart muscle, which induces formation of collateral vessels in the myocardium. This process may forestall or prevent a heart attack. Of course, a rupture of the atheromatous fibrous cap may result in a thrombus-induced myocardial infarction.

Effects on the Brain

Atherosclerosis of the arteries supplying the brain is the most common cause of cerebrovascular accident and transient ischemic attacks (TIAs). Atherosclerosis has a tendency to affect the cerebral circulation, most commonly at the carotid bifurcation. Atherosclerosis of the carotid arteries may cause a major occlusive event that yields a hemispheric stroke. Small emboli may break off of the arterial atheroma and occlude smaller cerebral vessels, resulting in TIAs.

Effects on the Kidney

Atherosclerosis can directly affect the kidneys by causing renal artery stenosis. This condition causes a reduction of blood flow to the kidneys that results in chronic renal failure. Atherosclerosis has a tendency to affect the proximal portions of the renal arteries and is a frequent site of atheroembolic disease.

Effects on the Retina

Arteriolar sclerosis of the retinal arteries is demonstrated by an increase in the light reflex. As the general body-wide atherosclerotic condition advances, the retinal arterial light reflex evolves from a healthy red to a pink color. As the arteriole wall thickens, the color of the vessel becomes progressively lighter until it turns white, which indicates almost complete occlusion of the retinal vessel. A branch retinal artery occlusion results in retinal ischemia to the area fed by the vessel. A permanent scotoma may result in the part of the visual field that is served by the area of infarcted retina. A central retinal artery occlusion results in sudden, painless, and complete visual loss in the involved eye. The eye will demonstrate a relative afferent pupillary defect, or Marcus-Gunn pupil. Ophthalmoscopy in this case reveals a pale fundus with a cherry-red spot in the area of the macula that is fed by the underlying choriocapillaris. Retinal arterial occlusions may be caused by a primary atheromatous lesion or a secondary embolic plaque dislodged upstream, most commonly from the carotid artery.

Effects on the Peripheral Circulation

Atherosclerosis has profound effects on the peripheral circulation. This condition is a common cause of intermittent claudication, a term used to describe exertion-induced limb pain that causes limping and periods of prolonged rest. In patients with gangrene who are often confined to bed rest, atherosclerosis often jeopardizes the healing of the wound. Atherosclerosis often complicates peripheral wound healing and increases the likelihood of limb amputation.

Prevention of Atherosclerosis

The identification of risk factors has molded the concepts inherent in preventing atherosclerosis. Modifiable risks include lipid disorders, hypertension, diabetes, and lifestyle choices. Unmodifiable risks include gender, genetics, and postmenopausal state.

Modifiable Risk Factors

Control of Lipid Disorders

Lipid abnormalities are the single greatest risk in the development of atherosclerosis. Laboratory testing to pinpoint derangements in lipid metabolism include a fasting total cholesterol, triglyceride, HDL, and LDL level. Another recently identified marker for systemic atherosclerosis is C-reactive protein (CRP), which has shown value in identifying patients at high risk for vascular events.

Pharmaceutical intervention to lower LDL levels has been shown to reduce atherosclerosis in both men and women. The use of statin medications has been shown to reduce cardiac events and total mortality in a population of patients with hypercholesterolemia who have never had a heart attack. In a group of patients who had normal cholesterol and LDL levels, but low HDL levels and no previous heart attack, a statin medication also reduced coronary events. A significant amount of evidence supports the use of drug therapy to prevent heart attacks and strokes in patients with hypercholesterolemia. Drug therapy does not reduce the size of the atheroma, however, as might be expected. Angiographic studies reveal that after the implementation of cholesterol-lowering medications, the luminal size of the involved artery does not change. This finding supports the concept that the atheroma is stabilized but does not shrink in size. Stabilization is most likely achieved by medicinal stimulation of lipid egress from the atheroma, or by promoting the endothelial production of the beneficial radical nitric oxide (NO).

Because oxidation of the LDL molecule in the atheroma is believed to be the stimulating event that promotes foam-cell formation and induces inflammation in the artery wall, mitigation of this process would theoretically reduce atherosclerosis. Oxidation of the LDL molecule is suppressed by antioxidant molecules, but to date few controlled trials support replacing established pharmaceutical treatment with antioxidant therapy.

At present the lowering of lipid levels is best achieved by a combination of statin medications with a supplementation of antioxidants, a reduced fat intake, weight loss, and an exercise program.

Control of Hypertension

A relationship appears to exist between systemic hypertension and the evolution of atherosclerosis. Antihypertensive therapy theoretically should reduce atherosclerosis, and indeed some studies show that a reduction in blood pressure will reduce coronary risk. Unfortunately, the thiazide derivatives and beta-blocking agents used in the majority of hypertensive cases have an adverse effect on the cholesterol profile. In cases of systemic hypertension in which advanced atherosclerosis is a possibility, the use of angiotensin-converting enzyme (ACE) inhibitors, which are lipid-neutral, may be advantageous.

Control of Diabetes Mellitus

The most common cause of death among the population of diabetics is atherosclerosis. Type II diabetics have an elevated risk of a major cardiovascular event

because of the abnormal lipid profile associated with insulin resistance. Known as diabetic dyslipidemia, this condition is characterized by low HDL, elevated triglycerides, and LDL particles that are dense and atherogenic. Theoretically, strict glycemic control in the diabetic patient should be beneficial in reducing renal effects and the development of retinopathy from atherosclerosis. Evidence to support this theory is lacking, however. Because other factors involved in diabetes may contribute to the development of atherosclerosis, medical intervention is therefore necessary to optimize the lipid profile. Strong experimental evidence supports the use of statin medications to reduce the risk of atherosclerosis even in diabetics with normal lipid profiles. The American Diabetes Association recommends such aggressive treatment and suggests that the type II diabetic should have an LDL level no greater than 100 mg/dl.

Homocysteine Control

A significant relationship has been established between hyperhomocysteinemia and coronary artery disease, but a direct relationship between elevated homocysteine levels and atherogenesis has yet to be established. Elevated homocysteine levels have been shown to result in thrombosis, however. Because plasma homocysteine can be modified by diet, the intake of folic acid to reduce homocysteine levels may be beneficial in eliminating this risk factor. No clinical trials to this date support the use of folate in reducing coronary events, however.

C-Reactive Protein

C-reactive protein (CRP) is an acute-phase reactant that serves as a marker for inflammation. This molecule indicates the presence of inflammation but may not actually take part in the process. A number of studies have shown that elevated CRP plasma levels can predict myocardial infarction risk. Whether elevated CRP actually reflects the inflammation present in atherosclerosis, or simply correlates with the outcome of acute coronary artery disease, is still uncertain, however. For example, elevated CRP may reflect extravascular inflammation that eventually promotes atherogenesis. Studies show that the reduction of CRP is desirable in reducing the risk of coronary artery events. Studies have show that statin medications effectively reduce CRP and that this use of antiinflammatory therapy may reduce atherosclerotic events.

Lifestyle Choices

Patients at risk for atherosclerosis as determined by diabetes, hypertension, family history, and clinical symptoms and signs should be counseled to limit or eliminate tobacco use. These patients should also consider weight reduction and dietary changes to reduce the intake of animal fat and increase the consumption of food products high in antioxidants. A minimum of 30 minutes of physical exercise daily can help reduce obesity and premature atherosclerosis. Combining these factors into a healthy lifestyle may delay the need for medical intervention in the patient at risk for vascular disease.

Unmodifiable Risk Factors

Gender

Males have an undeniable elevated risk profile for atherosclerosis when compared with premenopausal women. Because gender is an unmodifiable risk factor, the male patient should be considered at risk for atherosclerosis if he has diabetes, obesity, systemic hypertension, an abnormal lipid profile, a known family history of occlusive vascular events, or elevation in plasma levels of inflammatory markers or homocysteine. Male patients with such risk factors should be encouraged to exercise, lose weight, stop smoking, reduce fat intake, and consider vitamin supplementation to increase antioxidant consumption. The use of estrogen supplementation, which appears helpful in postmenopausal women, has been shown to increase mortality in men because of thrombus development.

Postmenopausal State

The rate of coronary events in women has been shown to escalate after menopause, caused in part by falling plasma levels of HDL. This decrease in HDL reflects the falling concentration of plasma estrogen, which has a harmful effect on the lipid profile. Although menopause is an unmodifiable risk, the use of estrogen supplementation has been shown to lower LDL and raise HDL plasma levels, which should result in a lower coronary risk. One long-term study in women who had already had one myocardial infarction, however, showed no vascular benefit of estrogen replacement therapy after 5 years of treatment. The use of statin medications has been shown to be as beneficial in reducing coronary risk in women as in men, however.

SYSTEMIC HYPERTENSION

Because high blood pressure (HBP) is often an asymptomatic disease, nearly one third of all cases in the United States go undiagnosed. When left untreated, chronic high blood pressure often leads to serious complications and death, usually as a result of renal and congestive heart failure. Yet systemic hypertension is easy to detect and is usually readily treatable. This discrepancy is most likely to the result of patient noncompliance. Patients with no symptoms may not seek out medical guidance, and even when the diagnosis of high blood pressure is established they may be reluctant to use medications. This behavior results in reduced diagnosis and treatment of a disease that can have lethal complications.

Essential Hypertension

Because so many systems are responsible for the maintenance of blood pressure, clinicians are sometimes unable to establish the cause of the hypertensive state. Essential hypertension is defined as high blood pressure with no definable cause, and is also known as idiopathic or primary hypertension.

Blood pressure is regulated by the renal, hormonal, vascular, and neurologic systems. As such, abnormalities in blood pressure may be multifactorial in nature and still manifest in the same way.

Secondary Hypertension

In this class of hypertensive patients, the etiology of the elevation in blood pressure can be identified. This condition is most often the result of renal disease, and involves the inability of the kidneys to handle sodium and fluids that ultimately leads to an increase in plasma volume. Kidney disease may also result in an alteration in arteriolar tone that results in hypertension.

Another known cause of secondary hypertension is primary aldosteronism, an adrenal cortical abnormality resulting in sodium retention. Aldosteronism may be caused by a tumor or bilateral adrenal hyperplasia.

Cushing's syndrome may cause secondary hypertension. In this disease large amounts of glucocorticoids result in the sodium-retention that ultimately leads to volume expansion.

Pheochromocytoma is often caused by an adrenal medulla tumor and results in an increase in epinephrine and norepinephrine. These compounds excessively stimulate adrenergic receptors, in which leads to peripheral constriction of blood vessels and a subsequent rise in blood pressure. In addition, the stroke rate will increase as will the volume of the heart exposed to elevated levels of these compounds. Visual field analysis of the patient with pheochromocytoma often reveals a bitemporal hemianopsia that is denser in the inferior field than the superior field.

Pregnancy-Induced Hypertension

Preeclampsia is pregnancy-induced hypertension. This condition is difficult to treat and usually does not require intervention in the second or third trimester if diastolic pressure is 95 mm Hg or below. Diuretics, salt restriction, and beta-blockers may have a profound wasting effect on the fetus. ACE inhibitors may also adversely affect the fetus. Calcium channel antagonists and hydralazine are most often used to treat pregnancy-induced hypertension. No known effects exist on the fetus from the use of these medications. Topical phenylephrine, used in its 2.5% form for routine pupil dilation and its 10% form for the breaking of posterior synechiae, may have profound hypertensive effects. Increased blood pressure from the use of these topical medications has been documented, although it is far more frequent with the 10% dose. To minimize the effect of topical phenylephrine on the systemic blood pressure, it is advisable to use punctal occlusion for a minute after insertion of these eye drops.

Risk Factors in High Blood Pressure

A genetic role in the genesis of HBP is reflected in family studies that show a propensity towards hypertension among siblings of hypertensive parents. In addition, certain identifiable genetic defects have been positively linked to the susceptibility of systemic hypertension. So much variability in the expression of the disease and the phenotypic makeup of the patient exists, however, that genetic studies of HPB remain extraordinarily challenging.

Other risk factors that encourage HBP include obesity, occupation, and salt sensitivity in the 60% of HBP patients who are sensitive to sodium intake. Elevated sodium levels will lead to fluid retention and an increase in blood volume. This process consequently increases the force that the heart must exert to pump this increased blood volume, thus raising blood pressure.

Blood pressure is also related to the presence of renin, a kidney enzyme that ultimately is responsible for producing angiotensin II, and the secretion of which is related to blood volume and sodium intake.

An elevation in the insulin plasma level, or hyperinsulinemia, raises blood pressure by increasing sodium retention, increasing sympathetic nervous response, and changing the cell's membrane ion transport mechanism.

Prognostic Indicators in High Blood Pressure

Systemic hypertension identified in a younger patient has a poorer prognosis than in an older individual. Similarly, HBP diagnosed in an African-American patient tends to have a worse outcome. In the black patient, HBP is more difficult to treat, has a worse ultimate prognosis, and a reduced life expectancy. Males are at greater risk for HBP than females. Systemic hypertension is complicated by smoking, diabetes, obesity, hypercholesterolemia, and excessive alcohol intake. These risk factors aggravate the complications of systemic hypertension and result in premature renal, cardiac, retinal, and cerebrovascular disease.

Effects of Systemic Hypertension

Heart Effects

Because HBP causes an increased workload on the heart, the cardiac muscle compensates with a stronger stroke force that results in left ventricular hypertrophy. This condition is characterized by an increase in the thickness of the ventricle wall. As the left ventricular wall thickens, the function of the chamber deteriorates and blood circulation is compromised. The result is congestive heart failure. As the heart muscle itself becomes poorly oxygenated, angina pectoris, or chest pain, may occur. The most common cause of death in the hypertensive patient is myocardial infarction or congestive heart failure.

Effect on the Brain

The most common and earliest neurologic symptom of systemic hypertension is the occipital headache. These most often occur in the morning. In addition, other neurologic signs of HBP include vertigo, dizziness, lightheadedness, and dimming of vision. Ultimate damage to the brain results from cerebrovascular accident, wherein HBP may contribute to the vascular occlusion or hemorrhage. Hypertension can accelerate atherosclerosis of the cerebrovascular vessels and result in an occlusive stroke secondary to cerebral infarction. If hypertension is present with cerebral vascular microaneurysm, then a resultant stroke is the result of hemorrhage.

Effect on the Kidney

Hypertension causes a decrease in glomerular filtration rate and tubular dysfunction, resulting in blood and protein in the urine. Renal failure results in 10% of deaths caused by hypertension.

Effect on the Retina

Prolonged systemic hypertension results in retinal vascular effects (sclerosis, constriction, crossing changes, vessel narrowing, and microaneurysms) and retinopathy (hemorrhages and exudates) and papilledema. Observation of hypertensive retinopathy has been helped by the development of slit-lamp stereo ophthalmoscopy using high-powered, hand-held condensing lenses.

Vessel Narrowing

Chronic hypertension with a significant elevation in diastolic pressure has been directly related to the narrowing of the caliber of the vessel. A high diastolic pressure causes an increase in intraluminal pressure within the central retinal artery or retinal arteriole. Arteriole narrowing is best judged by comparing the caliber of the artery with that of an adjacent retinal venule.

The duration of hypertension has been directly related to the amount of vessel sclerosis. Atherosclerosis of the retinal arteriole is modified by the height of the diastolic pressure and evolves from vascular hypertonus to vessel wall hyperplasia to eventual fibrosis. The vascular wall is thickened with elastic and fibrous tissue that causes luminal narrowing. Atherosclerosis of the retinal arterioles proceeds from a bright luster of the vessel, through a burnished copper color, to a silver reflex (Figure 6-1). Complete occlusion of the vessel precludes demonstration of any visible bloodstream.

Localized, symmetric narrowing of the retinal arteriole is characterized by abrupt increases and decreases in the caliber of the vessel. These focal constrictions are most commonly seen in patients with a diastolic blood pressure greater than 110 mm Hg. But these focal constrictions are related to hypertonus and not atherosclerosis and therefore may disappear with reduction in blood pressure.

Arteriovenous Crossings

The retinal arteriole and venule share a common adventitial sheath in the area where they cross each other. Compression of the vein will cause venule deviation and vein humping. As the compression continues, blood backs up distal to the crossing and causes a localized dilation of the vein. Proximal to the point of compression, the vein narrows when compared with the distal vein. This process is known as "banking," because it is reminiscent of putting coins in a bank. The alteration of light transmission from the image of the vein through the thickened sclerotic vessel wall accounts for concealment of the vein. In this case, sections of the venule adjacent to the artery appear to disappear before crossing under the sclerosed vessel wall.

Microaneurysms

A small out-pouch of a venule wall may form because of increased luminal pressure in patients with retinal arteriolar sclerosis and hypertensive retinopathy. The

FIGURE 6-1 ■ Retinal arteriosclerosis secondary to long-standing systemic hypertension.

microaneurysm may be the direct result of an increase in pressure within the lumen of the venule when compression from a sclerosed arteriole causes "banking" of the vein. In this case, the microaneurysm will typically form on the proximal, or high-pressure, side of the vessel crossing. Microaneurysms may also form from anatomical defects in the walls of the retinal arterioles. Microaneurysms form most commonly in the walls of capillaries in patients with diabetes, followed by those with hypertensive retinopathy. These blood vessel irregularities are often associated with cotton-wool spots, but can occur in patients with no apparent underlying systemic disease. Microaneurysms are difficult to visualize and are best detected on fluorescein angiography.

Hemorrhages

The most common retinal hemorrhage associated with hypertensive retinopathy occurs superficially in the nerve fiber layer (Figure 6-2). Because the blood spreads easily between the nerve fibers, the hemorrhage takes on a streaked appearance and is termed a flame-shaped hemorrhage. This hemorrhage is a result of chronic hypertensive damage to the capillary wall endothelium that allows extravasation of plasma from the lumen into the extracapillary space. Flame-shaped hemorrhages may lead to macular edema and subsequent vision loss.

Cotton-Wool Spots

When chronic hypertension and arteriolar sclerosis combine to cause arteriole occlusion, focal ischemia results in the formation of a soft exudate known as cotton-wool spots. The cotton-wool spot represents a small area of capillary closure with resultant nerve fiber layer swelling. Histologically, degeneration exists of the axons in the inner layer of the retina. Grossly, they appear as large, feathery-edged whitish lesions located in the superficial retina of the posterior pole. Microaneurysms are often associated with the blurry edges of the cotton-wool spot. The cotton-wool spot resolves in several weeks when the involved capillary channels reopen. A glial scar is usually associated with the area of a resolved cotton-wool spot.

Macular Star

Yellowish-white exudates accumulate in the macula in hypertensive retinopathy and take on the appearance of a star (Figure 6-3). These radiating lines of exudative material are deposited in Henle's layer and are deep to the retinal blood vessels. They form focal leakage of end-arterioles or capillaries that have been damaged from chronic hypertension and arteriolar sclerosis.

Papilledema

Unilateral swelling of the optic nerve head is known as disc edema and results from direct effects on the optic nerve or its blood supply. Papilledema, or bilateral disc edema, is the result of either intracranial pressure, which is rare in hypertension, or direct effects on both optic nerves. In cases of hypertensive retinopathy, the finding of a swollen optic nerve head indicates the presence of malignant hypertension and is an ominous sign. It is caused by arteriolar occlusion with subsequent ischemia and extravasation of plasma elements into the optic nerve head (Figure 6-4). Leakage of plasma may induce a pressure gradient within the optic nerve that results in reduction of axonal transport and subsequent nerve head swelling. Capillaries within the nerve head become tortuous, dilated, and engorged. Papilledema may result from encephalopathy,

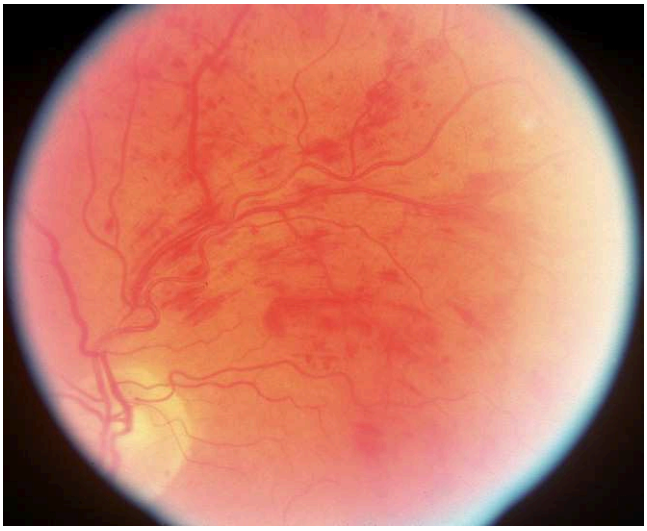

FIGURE 6-2 ■ Flame-shaped hemorrhages in a patient with chronic systemic hypertension resulting in a branch retinal vein occlusion (BRVO).

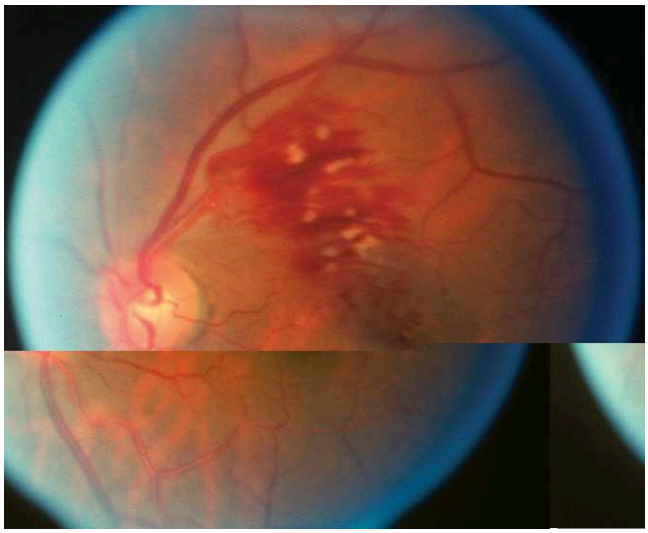

FIGURE 6-3 ■ Hypertensive retinopathy demonstrating hard exudates and flame-shaped hemorrhages.

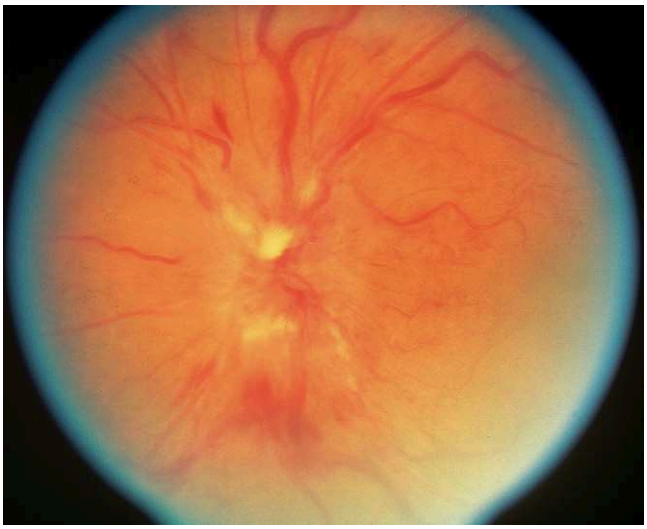

FIGURE 6-4 ■ Disc edema in a case of central retinal vein occlusion (CRVO) secondary to malignant hypertension. Note blurring of the disc margin, extensive flame-shaped hemorrhages, and the presence of cotton-wool spots.

and is frequently accompanied by headaches, nausea, vomiting, and convulsions. Patients with malignant hypertension require hospitalization and slow reduction of their systemic blood pressure.

Drug Treatment of Systemic Hypertension

Diuretics

Diuretic medications are known as thiazides and their use results in a decrease in volume within three days of initiation of therapy. They are the single most important class of antihypertensive medications currently available and have few side effects. Nonetheless, clinicians are currently reluctant to use this class of medications because of the loss of potassium, retention of uric acid, exacerbation of diabetes, and adverse lipid effects. Also, patients may complain of an increase in urination, particularly early in the treatment. Despite these disadvantages, recent studies confirm a significant reduction in morbidity and mortality in hypertensive patients who begin diuretic therapy. Medications in this class include furosemide, amiloride, and hydrochlorothiazide (HCTZ).

Antiadrenergic Agents

Alpha-Receptor Agonists

These medications may act on the central vasomotor center of the brain by stimulating alpha-receptors, thus reducing sympathetic outflow. This decrease in turn reduces blood pressure. A reduction in cardiac output and heart rate also occurs. Clonidine is an example of a central acting antiadrenergic agent that is useful in mild-to-moderate hypertension and hypertension secondary to renal disease.

Alpha-Adrenergic Receptor Blockers

These drugs block the peripheral alpha-adrenergic receptor sites. These drugs are rarely used because of the tolerance to the medication that eventually develops.

Beta-Adrenergic Receptor Blockers

Often used as first-line agents for systemic hypertension, these medications act to block the sympathetic effects on the heart. A lowering of cardiac output and arterial pressure results. Examples of this class include propranolol, metoprolol, atenolol, timolol, and betaxolol. These agents should never be used in cases of congestive heart failure or asthma because they may worsen these conditions. In addition, beta-blockers may mask the signs of hypoglycemia. Nonetheless, the use of beta-blockers has been shown to significantly reduce the morbidity and mortality of hypertensive patients.

Vasodilators

These agents relax smooth muscles to reduce arterial resistance. Hydralazine is the most frequently prescribed drug of this class, because it is a useful adjunct in the treatment of moderate to severe hypertension. As a class, however, these medications have significant limitations and are never used as a first-line therapy.

ACE Inhibitors

This class of drugs acts to inhibit angiotensin I from converting to angiotensin II-ACE. ACE is a potent vasoconstrictor, and inhibiting its development will result in vasodilation and reduced blood pressure. These drugs include captopril and minoxidil, which are excellent adjuncts in the treatment of moderate-to-severe hypertension. This class of medications has significant side effects, including cough, rash, fever, angioedema, and renal failure.

Angiotensin-Receptor Agonists

These medications are similar to ACE inhibitors and act by binding to angiotensin II receptor sites. Losartan and valsartan are two such drugs.

Calcium-Channel Agonists

These agents modify calcium entry into the cells by binding to receptor sites. This action results in vasodilation and a reduction in blood pressure. These drugs include nifedipine and amlodipine.

Treatment Protocol

The goal of drug therapy in systemic hypertension is to reduce arterial pressure to normal levels while avoiding unwanted side effects. One significant study

showed that two agents were needed to reduce diastolic blood pressure below 90 mm Hg in 70% of cases. Although no one therapy protocol should be used in all patients, clinical studies have shown that for the majority of patients, the following clinical approach is appropriate.

Early Hypertension

The clinician should begin by prescribing a diuretic medication. The lowest dose possible should be used to minimize side effects, and if two drugs are used, one should almost always be a diuretic.

Ineffective Diuretic Therapy

If the hypertension is not improved by a diuretic, it is essential to add a second medication. Appropriate adjuncts to diuretic therapy include a beta-blocker, ACE inhibitor, or angiotensin receptor agonist.

Diuretic Intolerance

If the hypertensive patient cannot tolerate the side effects of a diuretic, then a calcium channel-blocking agent such as verapamil is usually effective.

Ineffective Calcium Channel-Blocker Therapy

If the calcium channel-blocker is insufficient to lower systemic hypertension to the desired level, then a second agent is added. These agents usually include either an ACE inhibitor or beta-blocker.

Continued Ineffective Therapy

If two antihypertensive agents fail to lower blood pressure to normal, then the dosages should be increased to full strength. Salt intake should be minimized, and a third blood-pressure agent may be added to the therapy regimen.

Triple Therapy

This treatment approach usually includes a diuretic, ACE inhibitor, and a vasodilator (hydralazine). The medication dosages should be minimized to determine the lowest amount of medication necessary to allow normalization of blood pressure.

CORONARY ARTERY DISEASE

Atherosclerosis is the primary cause of the ischemia to the heart muscle. Ultimately, this process may result in angina, ischemic heart disease (IHD), and myocardial infarction.

Ischemic Heart Disease

When significant atherosclerosis of the epicardial coronary arteries exists, the perfusion of oxygen to the heart muscle may be inadequate. The result is ischemia, which results from an imbalance between the demand by the heart muscle for oxygen and the amount of blood supplied by the coronary arteries.

Ischemic Heart Disease Risk Factors

Atherosclerosis is the most common cause of IHD, although anemia, left ventricular hypertrophy, congenital malformations of the coronary arteries, and abnormal constriction of the coronary arteries may contribute to reduced perfusion. An atherosclerotic plaque that develops within a coronary artery reduces blood pressure beyond the point of constriction. Coronary arteries may adjust to a certain degree, but eventually cannot compensate for the reduced blood pressure distal to the atheroma. Once the coronary arteries are maximally dilated to compensate for the lowered perfusion of blood through the stenosed lumen, myocardial blood flow then becomes entirely dependent on the blood pressure distal to the plaque. When this perfusion pressure is lower than the demands of the heart muscle, then ischemia may result.

Ischemic Effects

Total occlusion of the coronary artery by an atheroma results in instant and catastrophic failure of the heart muscle. More commonly, partial occlusion of the coronary arteries will result in intermittent and exertion-induced chest pain (angina pectoris). Transient myocardial ischemia results in chest discomfort described as a squeezing, smothering, or choking, sensation. These episodes of stable angina pectoris may be related to exertion or emotion, and often occur after periods of stress, anger, or exercise. Unstable angina pectoris occurs during rest or at night during sleep. Patients with symptoms of angina pectoris should undergo a thorough history, stress test, physical examination, laboratory testing (lipid profile, x-ray), electrocardiogram (ECG), and coronary arteriography.

Stress Test

IHD is best diagnosed with the stress test. The 12-lead ECG is measured before, during, and after exercise on a bicycle ergometer or treadmill. As the patient is physically stressed, the workload is increased and the symptoms of IHD, blood pressure and ECG are measured. The test is stopped if there is chest pain, shortness of breath or significant changes on the ECG. An increase in blood pressure and heart rate usually occurs when the work load is increased. If the patient cannot exercise because of peripheral vascular disease or claudication, then the stress test may proceed with a radioactive tracer that can detect myocardial ischemia. ECG indications of IHD along with a drop in blood pressure during the stress test are ominous signs.

Two-Dimensional Echocardiography

Evaluation of the left ventricle using two-dimensional echocardiography can pinpoint ventricular wall abnormalities. Echocardiography (ECG) can be performed during stress testing to aid in the diagnosis of IHD.

Coronary Arteriography

Coronary arteriography (CA) images the coronary anatomy and is used to detect sclerotic plaques and obstructive lesions. When CA is combined with imaging of the left ventricle, the functioning of this chamber can be assessed. CA is indicated in patients who have IHD, angina pectoris, a need for bypass surgery, or a history of AMI.

Prognosis of Ischemic Heart Disease

The prognosis of the patient diagnosed with IHD depends on the location and severity of the coronary artery stenosis as determined by coronary arteriography, the functioning of the left ventricle as determined by left ventriculography and the severity of myocardial ischemia as determined by adjunct cardiac testing including the stress ECG and two-dimensional echocardiography. Patients with IHD are at greater risk of a major cardiovascular event if they have recently had angina pectoris, cardiac enlargement, left ventricle impairment, abnormal resting ECG, and a drop in blood pressure during a stress test revealing myocardial ischemia at low workloads.

Treatment of Ischemic Heart Disease

The goals of therapy for myocardial ischemia are coronary revascularization, pain management and medical intervention for angina, and reduction of the impact of atherosclerosis of the coronary arteries.

Atherosclerosis Risk Factors

The patient should be informed of the risk factors for atherosclerosis and be encouraged to lose weight if obesity is an issue, control any hypertensive, diabetic, or hyperlipidemia conditions, and cease smoking.

Treatment of Angina Pectoris

Medical management of angina pectoris includes the use of nitrates. This class of drugs causes venodilation, which reduces oxygen demand on the myocardial muscle. Of these agents the most notable is nitroglycerin, which is best absorbed through the mucous membranes and is administered as a sublingual tablet. Sublingual nitroglycerin is the most effective of all nitrate agents for the quick relief of acute angina pectoris. Beta-blockers can also be used to treat angina pectoris, because they reduce myocardial oxygen demand by lowering the heart rate and contraction strength of the heart. Because calcium antagonists are coronary vasodilators, they reduce myocardial oxygen demand and arterial blood pressure. The regular use of aspirin has been shown to reduce coronary events in asymptomatic adult men and those with ischemia after MI by interfering with platelet formation.

The surgical management of IHD includes techniques to allow coronary revascularization. These techniques include percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).

PCI makes use of a stent placed into a stenotic coronary artery, which provides adequate vessel dilation and relief of angina. This method is commonly used in patients with angina pectoris who have evidence of myocardial ischemia on testing. PCI is usually limited to patients with single-vessel or two-vessel atherosclerotic lesions. Patients with three or more occluded vessels are better helped by CABG.

CABG is performed by placing a transplanted saphenous vein between the aorta and the coronary artery distal to the occlusion. Even more preferable is the anastomosis of the radial artery or mammary artery distal to the coronary artery occlusion. The surgery is safe, with occlusions of the grafts occurring in approximately 10% to 20% of cases after 1 year. Angina is completely relieved in 90% of cases. CABG provides relief of symptoms that are a result of stenoses of several epicardial coronary arteries.

Acute Myocardial Infarction

More than one million heart attacks occur in the United States every year, and nearly one third result in death before the individual is transported to the hospital. Age is a significant risk factor contributing to the acute myocardial infarction (AMI) mortality rate. For example, approximately 3% of all patients die within 1 year of their first AMI. But in those older than 75, the percentage of deaths 1 year after the initial AMI rises to approximately 30%, with two thirds of these patients having died within the first month.

Pathophysiology

Atherosclerosis causes a slowly developing stenosis of the coronary arteries. As the vessel lumen narrows, a network of collateral blood vessels develops and prevents an AMI by bypassing the stenosis. This process is the reason that chronic coronary artery stenosis rarely results in an AMI. Rather, an AMI is more commonly caused by an acute thrombosis. In this situation, the fibrous cap covering the atheroma breaks, and coagulation substrates from the rich lipid core of the lesion leach into the surrounding plasma and initiate thrombogenesis. Platelet aggregation at the site of vascular injury is potentiated by such substances as collagen, epinephrine, and serotonin. Other chemicals released at the site of

thrombogenesis potentiate thrombogenesis, prevent thrombolysis, and cause local vasoconstriction. Eventually the involved coronary artery becomes occluded by an aggregation of fibrin and platelet cells. Risk factors for the formation of thrombogenesis include hypertension, cigarette smoking, and an at-risk lipid profile.

Symptomology

Approximately one half of all cases of AMI have no precipitating factors, and in the remaining cases a preexisting physical state can be identified. Such precipitating factors for AMI include stress, physical exercise, strong emotions, or the presence of illness. Most patients report pain as the initial symptom of AMI. The pain is typically described as a deep, crushing, boring pain, and is often the worst pain the patient has ever felt. The pain most commonly occurs in the center of the chest with occasional radiation to the arms. Patients with AMI may also experience nausea, vomiting, anxiety, shortness of breath, and feelings of impending doom. Older patients, particularly those with diabetes, are at a greater risk of experiencing a painless AMI, with shortness of breath the only clinical symptom.

Clinical Examination

The patient experiencing an AMI typically is restless, anxious, and complains about substernal chest pain for longer than 30 minutes. The skin is pallid and the patient is perspiring, with coolness of the extremities. The pulse rate and blood pressure are usually normal. Auscultation will reveal the abnormal presence of third (S3) and fourth (S4) heart sounds to the examining physician.

Electrocardiogram Results

In an acute AMI that lasts from hours to seven days, the electrocardiogram (EKG) will reveal an ST-segment elevation with production of Q waves. A patient who complained of chest pain and has no ST elevation most often has unstable angina. In a patient with ST elevation and chest pain, the patient most often has had a Q-wave MI. In some cases the patient may have had a non-Q-wave MI, in which case detection of a serum cardiac marker suggests an AMI.

Laboratory Results

Infarction of the heart muscle leads to necrosis of the tissue. Damaged heart tissue releases specific proteins called serum cardiac markers that help diagnose AMI and the levels of which help determine management strategies. Elevations of creatine phosphokinase (CK) are seen within 4 to 8 hours of an AMI, but are not specific to heart damage. An elevation of CK must therefore be correlated to the patient's history and symptomology. More specific than total CK is the human creatine kinase isoenzyme test. Elevation of this marker helps determine the presence of an AMI. Other lab tests for AMI include cardiac–specific-troponin (cTnT) and cardiac–specific-troponin I (cTnI), and because of their specificity for damaged heart muscle, they have become the preferred serum cardiac markers. Myoglobin is released rapidly into the blood just hours after an AMI, but it lacks specificity and is excreted quickly, and thus is of limited diagnostic value.

Cardiac Imaging

The heart may be imaged using two-dimensional echocardiography. In this technique, ultrasound waves are bounced off structures of the heart and returned to produce cardiac images. Ultrasound of the heart after an AMI may reveal aneurysm, effusion, thrombus, abnormal wall motion, reduced left ventricular function, and right ventricular infarction.

Treatment

The majority of prehospital admission AMI deaths are caused by arrhythmias, particularly ventricular fibrillation. The immediate response to anyone exhibiting the symptoms of an AMI starts with recognition of those signs and the expeditious call for emergency medical attention.

Emergency Management

The ever-expanding use of portable defibrillators may help reduce the death rate of those AMIs that are caused by arrhythmias. Immediate transportation of the patient to the hospital by a trained emergency management team helps to identify the cardiac emergency and stabilize the patient. Once in the emergency room, pain control and triage become the priority. Lower-risk patients are relocated to the appropriate area of the hospital and higher-risk patients are immediately treated. Aspirin therapy has been shown to be effective in all cases of acute coronary syndromes. A 325-mg tablet is chewed in the emergency room to allow for buccal absorption. Oxygen may be given if the patient with an AMI is exhibiting poor ventilation-perfusion.

Pain Control

Sublingual nitroglycerin is administered in an effort to control chest pain in patients with AMI. An effective analgesic agent for diminishing chest pain is morphine, which may also replace the anxiety often associated with an AMI with feelings of well-being and even euphoria.

Management of Infarct Size

The sublingual nitroglycerin that is administered immediately in the emergency room after an AMI causes coronary vessel dilation and thus increases the myocardial oxygen supply. In addition, nitroglycerin decreases myocardial oxygen demand. After the administration of nitroglycerin, EKG results will help determine if the

AMI patient is a candidate for reperfusion therapy. Also known as thrombolytic therapy, this is a pharmacological intervention that attempts to lyse fibrin thrombi. Those patients who are not candidates for thrombolysis may have to undergo angioplasty or stenting (PCI).

Medical Management

Antithrombolytic Agents. Thrombolytic drugs act to convert plasminogen to plasmin. Plasmin then lyses fibrin thrombi, and by breaking down the blood clot the patency of the coronary lumen is restored. Such agents include streptokinase, reteplase (rPA), tissue plasminogen activator (tPA), and anisoylated plasminogen streptokinase activator complex (APSAC). Thrombolytic therapy should be instituted within 30 minutes to an hour after admission for an AMI. This therapy has been shown to reduce the rate of in-hospital death after an AMI by 50%. Heparin is often used in conjunction with, for example, tPA, in an effort to facilitate thrombolysis.

Beta-Adrenergic Blockers. Given intravenously, beta-blockers have been shown to control pain by reducing coronary oxygen demand. The use of beta-blockers has also been shown to reduce the in-hospital mortality rate of patients admitted for acute AMI.

Angiotensin-Converting Enzyme Inhibitors. ACEs should be prescribed within 24 hours to all patients with an AMI and congestive heart failure or hypertension.

Long-Term Pharmacotherapy. The goal of long-term therapy is the prevention of future thrombosis. Antiplatelet therapy includes aspirin and heparin. Long-term use of beta-blockers has been shown to reduce recurrent ischemia and reinfarction after an AMI. ACE inhibitors are added to the regimen of aspirin and beta-blockers to reduce mortality rate after an AMI.

Catheter-Based Coronary Revascularization

Percutaneous transluminal coronary angioplasty (PTCA) was first performed in 1977. In this technique, a catheter is introduced into the arterial system through needle puncture, and fluorescein dye is used to guide the catheter into the heart. The catheter has probes that analyze the functioning of the heart muscle. In addition, therapeusis is achieved by the advancement of a balloon up the catheter to the site of occlusion. The balloon is inflated thus compressing the atheromatous plaque against the coronary vessel wall. This has the effect of opening the lumen of the blood vessel. Now known as percutaneous coronary revascularization (PCR), this technique now is performed more frequently than coronary bypass surgery. To prevent re-stenosis of an involved coronary artery, the use of metallic scaffolds called stents may be inserted and expanded at the site of the lesion.

Coronary Artery Bypass Grafting

In coronary artery bypass grafting (CABG) the obstruction of the coronary artery is bypassed by the grafting of a section of saphenous vein between the aorta and the coronary artery distal to the obstruction. Even more preferable is a bypass that involves the surgical anastomosis of the radial artery distal to the coronary artery obstruction. The cardiology team follows significant protocols in deciding whether PCR or CABG is indicated.

CAROTID ARTERY DISEASE

Pathophysiology

Atherosclerosis and dissection of the carotid artery are the two most common diseases of this vessel. The site of the bifurcation of the carotid artery into its external and internal branches is often impacted by atherosclerosis. This condition is usually most severe in the first 2 centimeters leading from the bifurcation up the internal branch, and down along the walls of the common carotid artery. In addition to atherosclerosis, a large embolus from the pulmonary veins may lodge in the carotid artery, but this is a rare occurrence. Inflammation of the carotid vessel wall results in Takayasu's arteritis, a vasculitis that affects the extracranial carotid artery.

As the internal carotid artery enters the cavernous sinus, it is predisposed by its anatomical shape towards atheromatous disease. This condition may result in distal embolization with subsequent transient ischemic attacks or stroke.

The reduction of blood flow through the carotid artery results in cerebral ischemia. A reduction of blood to the brain of only 10 seconds will cause neurologic symptoms, but restoration of blood flow will result in only transient phenomenon. A reduction of more than a few minutes will result in permanent neurologic deficits because of infarction of brain tissue.

Clinical Manifestations

The clinical manifestations of a patient with internal carotid artery occlusion are variable depending on the cause of the cerebral ischemia and the amount of blood flow to the middle cerebral territory by the circle of Willis. For example, if blood flow through the circle of Willis is normal, the carotid occlusion may produce no symptoms. If the thrombus moves up the carotid artery and completely blocks the middle cerebral artery, however, then hemiplegia, hemianesthesia, homonomous hemianopsia, and aphasia may occur. Collateral blood flow that arises after arterial blockage often results in the development of partial syndromes. The homonomous hemianopsia that develops from occlusion of the

internal carotid artery is often an upper quadratic field loss, is bilateral, and often involves cortical blindness.

In 25% of cases of internal carotid artery occlusion, recurrent, transient periods of monocular blindness occur that act as a warning sign of an impending vascular event. These episodes occur because the internal carotid artery controls blood flow to the retina and optic nerve. All patients who complain of transient monocular "blur-outs" of vision, or fleeting moments of monocular "dimming" of vision, need a vascular evaluation to search for carotid artery stenosis, thrombus, or dissection. Bilateral visual TIAs may rarely be the result of bilateral carotid disease, but are more typical of vertebral-vascular disease.

Optometric Work-Up

Patients seen in the eye-care office with complaints reflecting such transient ischemic phenomenon should have an immediate visual field performed to rule out any stroke involving the visual pathway. The optometrist should make a diligent search of the anterior chamber for neovascularization of the iris that can arise from occlusion of 70% or more of the carotid artery (Figure 6-5). Significant carotid artery occlusion may yield an anterior ischemic syndrome, with ipsilateral rubeosis iridis and possible neovascular glaucoma. A dilated fundus examination using binocular indirect slit-lamp evaluation of the retinal arterial tree may reveal the presence of Hollenhorst plaques. These plaques may arise and break off from atheromatous lesions within the common carotid or internal carotid artery. The optometrist should diligently search for a carotid bruit using the stethoscope to auscultate the carotid region of the neck. If a retinal arterial embolus or bruit is discovered, the patient should be referred to his or her physician for a vascular work-up to rule out carotid disease. Even TIAs in the absence of retinal plaques and bruit should be referred for a vascular evaluation.

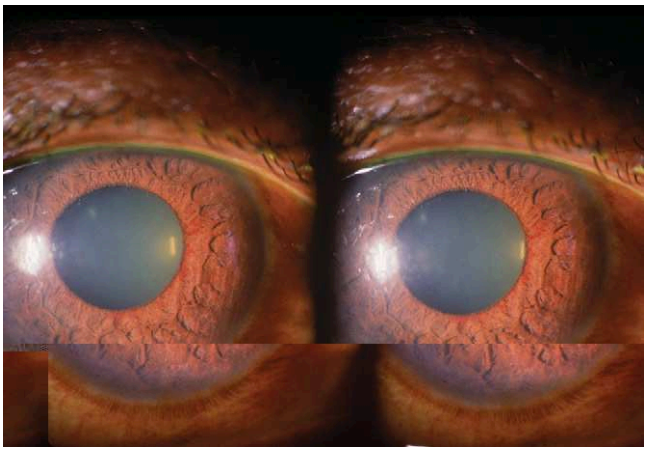

FIGURE 6-5 ■ Rubeosis iridis. This case of neovascularization of the iris occurred secondary to occlusion of the ipsilateral carotid artery, which led to an anterior ischemic syndrome.

Vascular Work-Up

The internal carotid artery is evaluated by Duplex ultrasonography, a technique that combines B-mode ultrasound imaging with Doppler ultrasound assessment of blood flow. In addition, x-ray cerebral angiography may be used to distinguish between complete and nearly complete carotid artery occlusion. Magnetic resonance imaging (MRI) angiography can detect extracranial internal carotid artery atheromatous plaques and stenosis of the intracranial portion of the internal carotid artery.

Treatment of Carotid Stenosis

The treatment of prestroke carotid artery stenosis includes pharmacological blood-thinning agents, such as aspirin, and the placement of stents within the lumen of the vessel. Balloon angioplasty with stenting can be performed on a stenotic carotid artery. This procedure is becoming more common in cases in which the atheromatous lesion affects the common carotid, subclavian, and vertebral arteries. Arterial bypass surgery is still experimental and involves extracranial-to-intracranial arterial arteries.

The carotid endarterectomy is the surgical approach to carotid vascular occlusion. This procedure is performed on stenosis of the vessel at the origin of the internal carotid artery in the neck. Shown to prevent stroke and TIA, carotid endarterectomy is performed to remove unwanted atherosclerotic plaques within the lumen of the carotid artery. The most appropriate candidate for carotid endarterectomy has multiple atherosclerotic risk factors, confirmed brain ischemia, and near occlusion of the internal carotid artery.

VERTEBRAL-BASILAR INSUFFICIENCY

In addition to the posterior cerebral arteries, circulation of blood to the posterior brain arises from paired vertebral arteries and the basilar artery. An atheroma or occlusion may block the basilar artery, and atherothrombic lesions may arise within branches of the vertebral artery. Vertebral-basilar insufficiency may result in TIAs and fainting (syncope), vertigo, and hemiplegia.

Occlusion of the vertebral artery may result in Wallenberg's syndrome, a constellation of signs including vertigo, ipsilateral Horner's syndrome, and ipsilateral facial and contralateral limb numbness.

Basilar artery occlusion may manifest as dizziness, diplopia, facial numbness, gaze paresis, a series of TIAs, internuclear ophthalmoplegia, and death.

Occlusion of the basilar artery often produces bilateral symptoms, whereas unilateral signs occur when a branch of the basilar artery is affected.

PERIPHERAL VASCULAR DISEASE

Pathophysiology

The most common cause of vascular disease of the extremities in patients older than 40 years of age is atherosclerosis. Peripheral vascular disease (PVD) occurs most often in diabetics, hypertensives, hyperlipidemics, cigarette smokers, and the elderly. In this disease there is segmental occlusion in the medium- and large-sized arteries, including the abdominal aorta, iliac, femoral, popliteal, tibial, and peroneal arteries.

Clinical Signs and Symptoms

Atherosclerotic occlusion of the more distal arteries leads to the common symptom of pain or fatigue in the muscles of the buttock, thigh, hip or calf. Known as intermittent claudication, the symptoms are made worse by exercise and are relieved by rest. Patients may complain of cold or numbness in the feet and toes. The physical examination may reveal absent pulses distal to the site of arterial obstruction. A bruit may be auscultated over the site of the obstruction. Hair loss and thickened nails may ultimately result from long-term peripheral circulatory disease. Patients may eventually develop peripheral neuropathy and ischemic neuritis from peripheral vascular disease.

Testing

The history and physical examination is usually sufficient to diagnose PVD. Doppler flow studies and duplex ultrasonography, along with stress testing are used to aid in the diagnosis and guide therapy. Arterial pressure within the legs is measured using sphygmomanometry.

Prognosis

Approximately half of all patients with PVD have significant coronary artery disease. One third of all patients with PVD are dead within 5 years, and half succumb after 10 years, most as a result of AMI.

Treatment

The patient with PVD must take extreme care of the foot and ankle by keeping the skin clean and free of injury. Risk factors towards atherosclerosis should be minimized by smoking cessation, control of blood pressure, cholesterol and lipid control, exercise, weight loss, and appropriate dietary habits. Aspirin reduces the risk of coronary events in patients with PVD, but like other medications, has not been shown to reverse peripheral vascular disease. Revascularization procedures, such as PTA and stent placement, have shown some success in keeping the peripheral arteries patent. The use of bypass grafts, depending on the location, has also had some success in improving survivorship.

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CHAPTER 7

Heart Disease

CHAPTER OUTLINE

In addition to coronary artery disease (see Chapter 6) some of the most significant diseases affecting the heart include rheumatic heart disease, disorders of cardiac rhythm, valvular disease, heart failure, and acute pericarditis.

RHEUMATIC HEART DISEASE

Just after World War II, half of the schoolchildren with heart problems were found to have had acute rheumatic fever. A total of 20,000 naval personnel were diagnosed with the condition. Now, in the early part of the twenty-first century, the condition is rare in industrialized nations, although scattered outbreaks have occurred in the United States since the 1980s.

Rheumatic fever occurs mostly in children, and is associated with lower socioeconomic lifestyles and crowded living conditions.

Rheumatic fever is caused by group A beta-hemolytic streptococci bacteria. The streptococcus may directly invade the heart tissue (although not enough evidence exists yet to support this hypothesis), or may cause a toxic effect on the myocardium. Even if these two processes do not occur and the infection has had no direct effect on heart tissue, inflammation may still arise because of an autoimmune effect.

The disease is diagnosed by the findings of fever, carditis (with cardiomegaly, sinus tachycardia, and specific heart sounds), polyarthritis (acute swelling of ankles, wrists, knees, and elbows), and, rarely, subcutaneous nodules. Laboratory testing is inconclusive, although streptococcal antibody tests may be used to show evidence of a group A streptococci infection.

Rheumatic fever may lead to a number of heart diseases, and is known to contribute to valvular stenosis and regurgitation.

Antistreptococcal antibody treatment is imperative in suspected cases of rheumatic fever. Long-term follow-up care involves frequent heart evaluations, and monitoring for any symptoms of valvulitis. The sequelae of rheumatic fever require treatments tailored to specific cardiac maladies.

DISORDERS OF HEART RHYTHM

Aberrant rhythm of the heart may be classified as arrhythmias of increased heart rate (the tachyarrhythmias) or those of decreased heart rate (the bradyarrhythmias). The important tachyarrhythmia to consider is tachycardia, which includes atrial fibrillation. Of the bradyarrhythmias, sinus node dysfunction and AV conduction disturbance are most significant.

The Tachyarrhythmias

Tachycardia is a heart rate of greater than 100 beats per minute, and is usually a physiologic response to abnormal demands on the heart, such as exercise or disease states. If three or more abnormal

electrocardiogram (ECG) complexes are noted, during this period of tachycardia, then the condition is considered a tachyarrhythmia.

Atrial Fibrillation

The most common form of tachyarrhythmia is atrial fibrillation (AF). This condition often occurs during exercise, emotional distress, or as a consequence of rheumatic heart disease. AF can cause symptoms of angina pectoris, syncope, embolization, fatigue, palpitations, and anxiety. During a period of AF, disorganized atrial activity occurs as detected on an echocardiogram (ECG). The heart rate may be 350 or more beats per minute. The ventricular response to AF is irregularly irregular.

AF may lead to stroke in particularly high-risk patients. These patients include the elderly, those with a history of hypertension or diabetes, a past history of rheumatic fever, or congestive heart failure (CHF).

Therapy for AF includes determination and treatment of a precipitating factor such as CHF, fever, alcoholic intoxication, or pneumonia or pulmonary emboli. Restoration of normal sinus rhythm can be achieved by electrical cardioconversion. Slowing of the ventricular rate may be achieved with beta-adrenergic blockers or calcium-channel antagonists.

Ventricular Fibrillation

Ventricular fibrillation (VF) is an arrhythmia that occurs in patients with ischemic heart disease and electrical accidents. After the onset of VF the patient experiences a quick loss of consciousness and death. VF is diagnosed on ECG readings as large, irregular undulations of varying amplitudes and rates.

Treatment of VF involves the use of antiarrhythmic drugs, including digoxin and quinidine, both of which can cause visual changes. In some cases, the use of a pacemaker for the electrical therapy of arrhythmia is preferable if drug therapy is not effective.

The Bradyarrhythmias

The normal heart rate is 60 to 100 beats per minute, and a rate less than 60 beats per minute is termed sinus bradycardia. This condition occurs when sympathetic tone is decreased by beta-adrenergic receptors or parasympathetic tone is increased, as happens with muscarinic receptors. Drugs, such as beta-blockers, may cause bradycardia. Optometrists who are prescribing a topical beta-blocker for the treatment of open-angle glaucoma should monitor the blood pressure and pulse of the patient. If the patient has low blood pressure, low pulse rate (less than 60 beats per minute), or if the patient is already on oral beta-blockers, the optometrist should notify the primary care physician before starting this patient on a topical beta-blocking agent. Topical beta-blockers may act synergistically with the systemic agent and cause overdose or exaggeration of the desired systemic effect.

SA Node Dysfunction

The main cardiac pacemaker is the SA node. Dysfunction of the SA node occurs in elderly patients and those with syncope, liver disease, hypothyroidism, and acute hypertension. This condition is characterized by dizziness, fatigue, and syncope. These symptoms are the result of long sinus pauses, or atrial asystole.

Diagnosis of SA node dysfunction is often confirmed by ECG readings and direct intracardiac recordings. Holter, or ambulatory, ECG monitoring helps to evaluate sinus node dysfunction.

Symptomatic SA node dysfunction is treated with implantation of a permanent pacemaker.

AV Conduction Disturbances

AV conduction disturbances occur when there is a disturbance of conduction for the sinus impulse to the ventricles. This can lead to heart block, syncope and death.

The AV node is supplied with sympathetic and parasympathetic input. The AV node is influenced by exercise, systemic diseases such as Lyme disease and sarcoidosis, drugs and neoplasm.

Acute AV conduction dysfunction is treated medically with intravenous atropine and isoproterenol. Pacemaker implantation may help stabilize the heart and relieve symptomatic bradycardia and certain forms of AV block.

VALVULAR DISEASE

Heart valve stenosis results in aortic, mitral, and tricuspid regurgitation, among other conditions.

Mitral Stenosis

The mitral valve controls blood flow from the left atrium (LA) to the left ventricle (LV). Stenosis of the mitral valve is almost always caused by rheumatic heart disease, which contributes to the formation of mitral stenosis (MS) approximately two decades after infection. Approximately 66% of all patients with MS are female.

The stenosis of the mitral valve is caused by calcification, which causes the mitral leaflets to become immobile. As the mitral valve opening reduces in size, left arterioventricular pressure increases, lung capacity decreases, and airway resistance increases, leading to the symptom of dyspnea, or shortness of breath.

MS is diagnosed on an echocardiogram and assessed by left cardiac angiography.

MS is treated with antibiotics as prophylaxis against streptococcus infections and infectious endocarditis.

Dietary sodium restrictions and oral diuretics may improve MS symptomology. Mitral valvotomy uses inflation of a balloon seeded across the mitral valve through catheterization to open the valvular orifice.

Mitral Regurgitation

In mitral regurgitation (MR), the mitral valves become hard, deformed, and retracted. This process causes regurgitation of blood from the LV back into the LA. MR can be caused by AMI, trauma, rheumatic heart disease, infective endocarditis, or mitral valve prolapse.

MR is detected on cardiac angiography because contrast material quickly appears in the LA after its injection into the LV.

Patients with MR typically experience fatigue and dyspnea on exertion.

MR is treated by prevention of exertional dyspnea by the restriction of stimulating activities. Sodium intake is reduced and diuretics may help. Surgical treatment for MR is not required unless there are symptoms. In patients with MR who are symptomatic, mitral valve reconstruction (MVR) may maintain LV function and reduce or eliminate symptoms.

Mitral Valve Prolapse

Also known as Barlow's syndrome or floppy-valve syndrome, mitral valve prolapse (MVP) is a common abnormality of the mitral valve. MVP may be caused by redundant mitral leaflet tissue or degeneration of the valve itself. MVP may be found to be associated with Marfan's syndrome and osteogenesis imperfecta, but in most cases the cause is never discovered.

Anatomically, MVP causes an increase in the size of the mitral valve annulus. This increase leads to regurgitation of the blood from the LV back into the LA. This process leads to stress and eventual ischemia of the heart muscle, the LV in particular.

MVP is most common in females between the ages of 14 and 30 years of age. This condition is typically benign and never progresses past the auscultated systolic click or murmur. The majority of patients have no symptoms for their entire lives.

Severe MR can result from MVP, however, and often causes arrhythmias, palpitations, syncope, and, rarely, sudden death. Transient ischemic attacks (TIAs) may occur because of emboli from the stenotic mitral valve (Figure 7-1).

Patients with MVP are usually reassured that, in the absence of symptoms, no treatment is necessary. Antiinfective agents may be used as prophylaxis against infective heart disease. Beta-blocking agents may reduce any chest pain experienced because of MVP. Symptomatic tachycardia resulting from MVP is treated with antiarrhythmic agents. Severely symptomatic patients with MVP may require surgical mitral valve repair. If the MVP results in TIAs, aspirin or other anticoagulants should be considered.

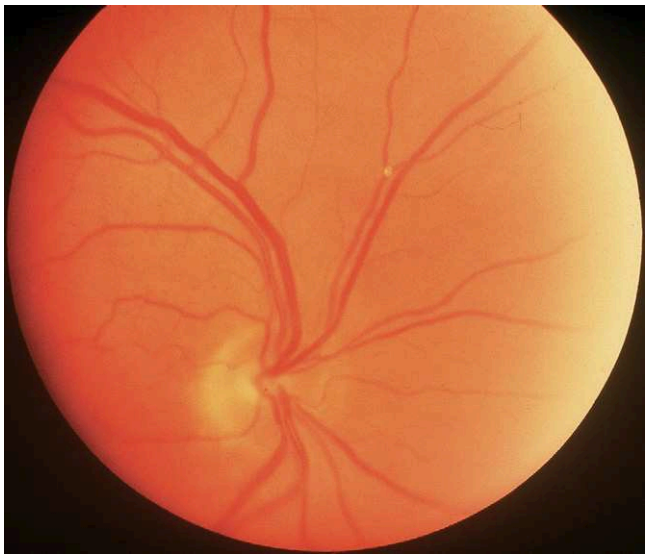

FIGURE 7-1 ■ Emboli in the retinal arterial tree causing transient ischemic attacks in a patient with mitral valve prolapse (MVP).

Aortic Stenosis

Calcification of the aortic cusps leads to valve thickening, increased rigidity, and a narrowed aortic opening. The effect of such stenosis is to obstruct LV outflow into the aorta. When this occurs, the LV becomes hypertrophied.

Aortic stenosis (AS) is caused by a number of conditions, including cardiac degeneration, endocarditis, a congenital malformation of the aortic valve, and inflammation of the aortic valve secondary to rheumatic heart disease.

Symptoms, including dyspnea, angina pectoris, and syncope, might not occur until late in the disease.

Patients with AS should avoid strenuous exercise, and salt intake should be restricted. Surgical treatment mandates aortic valve reconstruction (AVR). But the risks involved in AVR may forestall surgery if the patient is asymptomatic. AVR may improve angina pectoris, syncope, and LV decompensation.

Aortic Regurgitation

Aortic regurgitation (AR) is characterized by thickening, rigidity, and deformity of the aortic valve cusps. Because of this stenosis, the valve cusps lose their proper orientation during systole and diastole. This causes blood from the aorta to regurgitate back into the LV, which may lead to myocardial ischemia.

AR may occur associated with Marfan's syndrome or endocarditis. Patients often complain of tachycardia, palpitations, head pounding, dyspnea, and angina pectoris.

AVR may be necessary to relieve the symptoms associated with AR.

Tricuspid Stenosis

Tricuspid stenosis (TS) is rare in the United States and may be caused by rheumatic heart disease. Fatigue is the most common symptom in cases of TS. Poor blood flow from the right atrium (RA) to the right ventricle (RV) because of TS causes severe systemic venous congestion.

Diuretics help reduce total fluid volume and serve to relieve some of the systemic venous congestion. Tricuspid valve replacement (TVR) requires open heart surgery.

Tricuspid Regurgitation

Tricuspid regurgitation (TR) is seen in late tricuspid stenosis, heart failure, ischemic heart disease, and rheumatic heart disease. TR causes venous congestion but usually requires no treatment.

HEART FAILURE

The state of heart failure (HF) exists when the heart muscle no longer can pump blood at a rate appropriate to supply the metabolic needs of the tissues. HF is usually characterized by an inadequate contraction of the heart muscle and may be caused by viral infection, valvular disease, congenital heart disease, and coronary atherosclerosis. HF can be exacerbated by anemia, pregnancy, hypertension, arrhythmias, pulmonary lung infection, and rheumatic heart disease.

Patients in HF complain most often of dyspnea, as well as fatigue, weakness, nausea, confusion (caused by cerebral hypoxia), and anxiety. These patients may report swelling of the ankles and are typically out of breath when attempting to climb stairs. They may seek the counsel of an eye specialist because of fluid retention in the lower eyelids. Any new onset of lid swelling caused by fluid retention should prompt a referral to the primary physician for an evaluation to rule out heart failure.

HF is diagnosed by changes in the heart and lung sounds on auscultation, neck vein distention, enlargement of the heart, and two-dimensional echocardiography.

Treatment of HF involves identifying and eliminating the inciting cause (as in the case of an infective agent), correcting the underlying cause (using medical or surgical intervention), monitoring of the cardiac function, and control of progressive congestive heart failure. In general, the left ventricular load is controlled by use of ACE-inhibitors. Excessive fluid levels are controlled by the restriction of salt intake, weight reduction, and the use of diuretics. Cardiac glycosides, such as digitalis, can increase myocardial contractility and helps control HF. Topical beta-blockers for use as intraocular pressure-lowering agents should be avoided in HF, because systemic absorption of the drug may worsen the heart condition.

ACUTE PERICARDITIS

The pericardium is a serous membrane that surrounds the heart muscle. This membrane prevents sudden expansion of the chambers during exercise and helps atrial filling during ventricular systole. The pericardium also reduces friction between the moving heart and the surrounding tissues.

Inflammation of the pericardium is known as pericarditis and may be caused by infection, noninfectious entities, and autoimmune reactions.

Infectious pericarditis may be caused by viruses such as HIV and adenovirus infections. Bacteria, such as tuberculosis, and fungal infections are also known causes of infectious pericarditis.

Noninfectious pericarditis may be caused by AMI, neoplasm, elevated cholesterol levels, trauma and sarcoidosis, among others.

Rheumatic fever, ankylosing spondylitis, and certain drugs may contribute to the autoimmune basis of pericarditis.

The most common symptom of pericarditis is chest pain. Auscultation of the heart may reveal a pericardial frictional rub, a high-pitched grating sound heard on expiration. The ECG findings may reveal the presence of pericarditis.

Treatment of pericarditis is designed to eliminate the cause, such as an infectious agent, and control any effusion (or fluid leakage) from the swollen pericardium.

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CHAPTER 8

Kidney Disease

CHAPTER OUTLINE

The excretory function of the kidney helps to regulate the volume and composition of the plasma. The individual must excrete the end products of nitrogen metabolism, nonmetabolized dietary solutes, and excessive water volume, to preserve the internal environment of the body. In situations in which a deficit of water or solute exists, the kidneys act to conserve fluid and specific substances to prevent dehydration and preserve the intracellular and extracellular fluid compartments.

The processes of plasma ultrafiltration and reabsorption of the resulting filtrate occurs in the kidney and produces the volume and composition of excreted urine. Ultrafiltration of the plasma occurs at the glomerulus, and glomerulotubular balance is maintained by the reabsorption of filtered water and sodium salts by the renal tubules.

This chapter discusses the biological consequences of renal disease, including acute and chronic renal failure, proteinuria, systemic diseases and nephrology, injury, and nephrolithiasis. In addition, the effects of genetic disease and diabetes on kidney functioning will be explored. Renal therapy, including dialysis and transplantation, is an integral part of this discussion.

ACUTE RENAL FAILURE

In acute renal failure (ARF) a reduction in glomerular filtration rate (GFR) occurs within hours to days. This rapid inability to process plasma, water, and solutes results in the retention of nitrogenous waste products, most notably urea and creatinine. This disturbance of physiological homeostasis produces changes in the extracellular fluid volume and the acid-base balance of the internal environment.

ARF typically occurs without symptoms and is discovered when biochemical lab tests reveal a rise in plasma creatinine and urea concentrations. Usually characterized by oliguria, or a reduced urine output, ARF is reversible.

ARF is responsible for approximately one third of all admissions to intensive care units. It is a

complication of many serious conditions and contributes to significant in-hospital morbidity and mortality rates. ARF is associated with diseases that do not affect the renal tissues (prerenal ARF), diseases that do involve the renal tissues (intrinsic ARF), and, rarely, in cases of diseases associated with urinary tract obstruction (postrenal ARF).

Prerenal Acute Renal Failure

Accounting for slightly more than half of all ARF cases, prerenal ARF is characterized by mild-to-moderate renal hypoperfusion without kidney damage. This condition is typically caused by hypoperfusion caused by low blood volume (from trauma, hemorrhage, gastrointestinal fluid loss, and use of diuretics), low cardiac output, or systemic vasodilation. Prerenal ARF can complicate any disease that causes it. Renal hypoperfusion can be aggravated by the use of nonsteroidal anti-inflammatory drugs (NSAIDs), although their topical use with punctal occlusion should limit this serious systemic side effect.

Intrinsic Acute Renal Failure

Characterized by kidney damage, intrinsic ARF can be caused by toxins, allergy, infection, neovascular obstruction, glomerular disease, and tubular ischemia. The most common cause of intrinsic ARF is tubular sclerosis, and intrinsic ARF may result from cases of advanced atherosclerosis. Intrinsic ARF is characterized by renal hypoperfusion and may in rare cases lead to irreversible renal failure. The initial hypoperfusion usually occurs within hours to days of the instigating event, most commonly trauma, hemorrhage, volume depletion, or major cardiovascular surgery. Renal blood flow falls off and reduces the glomerular filtration process. Necrotic debris obstructs the kidney tubules because of the resulting ischemia. This obstruction disrupts ion transport and membrane integrity, leading to cellular death. Restoration of renal blood flow during this period may limit kidney tissue injury, and cell rejuvenation may occur in one to two weeks.

Diagnosis of Acute Renal Failure

ARF is diagnosed on the basis of laboratory testing that reveals elevated urea and creatine levels with anemia. Patients may experience thirst and dizziness, but ARF is typically asymptomatic. Physical examination may reveal tachycardia, dry mucous membranes, and reduced sweating. Retention of sodium, potassium, and water occur with ARF, with a consequent increase in volume with tissue swelling and weight gain. Eventual brain-tissue swelling with seizure activity may occur.

Treatment of Acute Renal Failure

ARF is treated best by avoiding the onset of renal hypoperfusion. Hypovolemia is treated by restoration of the intravascular volume after major surgery or trauma. As long as the primary hemodynamic abnormality is corrected, and fluid management is maintained, ARF is readily reversible. Approximately half of all patients with ARF die, but in most cases death is caused by the underlying disease and not the kidney involvement. The vast majority of patients who survive an episode of ARF recover renal function and live normal lives.

CHRONIC RENAL DISEASE

Chronic renal disease (CRD) is a long-term process of nephron destruction that results in a reduction in kidney mass and function. Early in this disease some kidney nephrons die, and the rest hypertrophy and sclerose. This process causes a reduction in GFR and, although asymptomatic, patient's urea and creatine serum levels rise. During the progression of the disease, severe renal insufficiency occurs when GFR drops even further. At this point, the patient is prone to urinary or respiratory infection and systemic hypertension. When GFR falls even further, permanent and widespread nephron destruction results in end-stage renal disease (ESRD), and the survival of the patient depends on renal replacement therapy.

As CRD progresses, nitrogenous waste products such as urea and creatine are retained, resulting in apothecia. Progressive renal insufficiency can cause functional derangement of multiple organ systems because of retention of toxins. Uremia results from failure of the kidneys to excrete toxins that are the products of protein and amino acid metabolism. Symptoms of uremia are variable but include anorexia, vomiting, headache, and fatigue.

Laboratory diagnosis will reveal fluid retention and acid-based disorders, metabolic acidosis, and abnormalities of bone, calcium, and phosphate. Other complications of CRD include anemia, congestive heart failure, peripheral vascular disease, and coronary artery disease.

The most common causes of CRD are systemic hypertension and diabetes mellitus, and the treatment of CRD is aimed at the underlying cause with the goal of avoiding ESRD. To avoid hyperfiltration injury, dietary protein is restricted and pharmaceuticals may be used.

Protein is degraded by the kidney to form urea, which must be excreted. CRD causes urea and other nitrogenous waste compounds to accumulate, thus resulting in uremia. Nephron injury may be slowed by the dietary restriction of protein-rich foods.

Medications to treat CRD are aimed at controlling systemic hypertension and offering nephron protection. The ACE inhibitors are particularly effective at performing these functions. With widespread renal destruction, eventual renal replacement therapy options include dialysis and kidney transplantation.

Dialysis

Dialysis serves to extend the life of the patient with ESRD. Patients with ESRD are candidates for dialysis if they have uremia, or other laboratory evidence of abnormalities caused by CRD. Hemodialysis aims to remove solutes from the sera. Blood from the patient flows through the dialyzer and urea is cleared from the system. Usually 12 hours per week of dialysis for a patient, divided into three equal visits, is needed for adequate treatment. The most common side effects of hemodialysis include systemic hypertension and muscle cramps.

Transplantation

The most effective renal replacement therapy for ESRD is kidney transplantation. It is least effective in elderly patients, those with metastatic cancer, or those with cardiopulmonary disease. Donor kidneys may come from living family members or cadavers, and the transplanted organ must have matching antigens of the human leukocyte antigen (HLA) major histocompatibility gene complex. After transplantation, immunosuppressive therapy is mandatory to prevent graft rejection but increases the risk of infection and malignancy. Such agents include azathioprine and, more recently, mycophenolate mofetil. Prednisone is a valuable adjunct in immunosuppressive therapy regimens, but use of this medication may increase the risk of glaucoma and posterior subcapsular cataracts. Cyclosporine is a powerful immunosuppressive agent usually used in conjunction with glucocorticoids to prevent renal tissue rejection.

PROTEINURIA

Proteinuria is an elevated serum protein level secondary to reduced protein renal excretion. The vast majority of the cases are benign, asymptomatic, and have an excellent prognosis. These cases can occur spontaneously during fever or exposure to environmental stress. All other diagnostic renal tests are normal. Benign proteinuria resolves without treatment.

If the proteinuria is persistent, then a renal lesion may be present. Proteinuria may be caused by diseases of the glomerulus and, in particular, glomerulonephritis.

SYSTEMIC DISEASE–RELATED NEPHROPATHY

Diabetic Nephropathy

The leading cause of ESRD is diabetic disease of the kidney. When diabetes causes kidney damage, hyperfiltration is present at first. Within 5 years of the onset of renal hyperfiltration a proteinuria becomes detectable on dipstick testing. Enlargement of the kidneys may result within a decade of onset. In patients who develop such nephropathy, more than two thirds develop diabetic retinopathy.

To slow the progression of diabetic nephropathy diet control, oral hypoglycemic agents and insulin are administered to control blood sugar. ACE inhibitors are used to control systemic hypertension. Poorly controlled diabetic nephropathy may yield ESRD, thus mandating the use of dialysis or transplantation.

Systemic Lupus Erythematosus Nephritis

Systemic lupus erythematosus (SLE) may cause isolated low-grade renal disease and CRD. The etiology of lupus nephritis is the deposition of immune complexes in the glomerular capillary wall. Diagnosis is made by renal biopsy. Blood laboratory studies may reveal a positive ANA and a positive anti–double-stranded DNA (dsDNA) antibody test. Some lupus nephritis cases do not require treatment. Advanced lupus nephritis cases may require glucocorticoids and cyclosporine therapy. This treatment usually controls acute glomerular inflammation.

Sjögren's Syndrome Nephropathy

Renal disease can occur in association with dry eyes in Sjögren's syndrome. Interstitial inflammation of the kidney tubules is the most common renal disease associated with Sjögren's syndrome. Glucocorticoids and cyclosporine have been used successfully to mitigate the Sjögren's nephropathy.

Nonsteroidal Antiinflammatory Drug—Related Glomerular Disease

Systemically ingested NSAIDs may produce ARF, kidney necrosis, and ESRD. If the oral administration of the NSAIDs is discontinued, then renal rejuvenation results in a return to normal kidney function. Topical NSAIDs pose little risk to patients of renal complications caused by poor systemic absorption and the typically short course of topical treatment. Patients with kidney disease who require topical NSAID therapy should use punctal occlusion while on these eye drops.

Sickle Cell Anemia Nephropathy

As many as one third of homozygotes for sickle cell anemia (SCA) have glomerular disease, with kidney hyperfiltration occurring in the first five years of life. Within 30 years approximately one third of survivors typically demonstrate proteinuria, and some develop ESRD. CRD may occur in patients with anemia and systemic hypertension. SCA-related retinopathy is a common association in SCA nephropathy.

Fabry's Disease

Glomerulosclerosis occurs as a late feature in Fabry's disease. Patients in their late teens to early 20s develop elevated urine lipids and proteins with high blood pressure and renal insufficiency. Corneal and lenticular opacities are a common feature of Fabry's disease. Kidney transplantation has been successful in some cases.

Gouty Nephropathy

Chronically elevated serum uric acid concentration may yield uric acid crystal deposits in the kidney. Such deposits cause inflammation of the kidney with lymphocyte proliferation. Renal fibrosis follows and results in insufficiency. Treatment with allopurinol will reduce serum acid levels and uric acid stone formation.

VASCULAR INJURY

The renal blood vessels may be compromised by systemic hypertension, atherosclerosis, embolism, and inflammation. If the lumen of the large renal vessels narrows, inadequate delivery of blood to the glomerular capillary network occurs. This process results in a reduced GFR.

Atherosclerosis or embolism may cause thrombosis of the major renal arteries. Acute onset of thrombosis causes trunk, side or back pain and fever. Blood tests show an elevation in renal enzymes (LDH is most reliable).

Surgical intervention may relieve the renal blood vessel occlusion, but approximately one quarter of patients die during an acute renal thrombosis.

Atherosclerosis of the renal artery may cause a shower of microemboli to occlude small kidney vessels, which may cause renal ischemia. Renal vein thrombosis may also occur.

KIDNEY STONES

Nephrolithiasis, or kidney stones, are composed of cysteine, uric acid, calcium salts, and struvite. Stones may be associated with gout. Stones may cause hematuria. If the stone breaks loose it may enter the ureter and cause excruciating back pain with fever. The passing of a stone is associated with pain and bleeding.

Stone removal is mandatory if pain, obstruction, or bleeding is present. Treatment involves the use of shock waves to fragment the stone and allow for passage (lithotripsy). Various therapeutic medications may prevent reformation of the stone.

OPHTHALMIC MANIFESTATIONS OF KIDNEY DISEASE

Patients with kidney disease may have manifestations in both the anterior and posterior chamber. Anterior chamber disorders associated with renal disease include band-shaped keratopathy and posterior-subcapsular cataract. The posterior manifestations include renal retinopathy, retinal detachment, Seigert's streaks, and Elschnig spots.

Band-Shaped Keratopathy

This uncommon anterior chamber manifestation of renal disease occurs because of elevated serum calcium levels. This state of hypercalcemia can result from renal failure, in which an elevated serum phosphorus level causes an alteration in the systemic calcium-phosphorus ratio. Calcium carbonate salts may deposit in the cornea near Bowman's membrane and extend across the interpalpebral zone. This hazy band can cause symptoms of halos, blurred vision, and foreign body sensation. Treatment of band-shaped keratopathy in symptomatic individuals involves removal of the deposition at the slit-lamp by using a scalpel and 2% to 3% sodium–ethylenediaminetetraacetic acid (NaEDTA) to expedite debridement. Phototherapeutic keratectomy with use of an eximer laser has been shown to be an effective technique to remove band keratopathy in some cases.

Posterior Subcapsular Cataract

This form of cataract is particularly detrimental to vision and is associated with the use of steroids and azathioprine in cases of renal transplantation. These immunosuppressive agents are used after transplantation to prevent or curtail tissue rejection. Cataract surgery is preferable to discontinuation of the immunosuppressive agent.

Renal Retinopathy

Patients in renal failure may exhibit a retinopathy consisting of atherosclerotic changes to the retinal arterioles, crossing changes, cotton-wool spots, and flame-shaped hemorrhages. This retinopathy is similar in

appearance to hypertensive retinopathy. Blood pressure readings will help to differentiate the true hypertensive retinopathy from renal retinopathy. Resolution of the retinopathy may occur with appropriate treatment of the renal disease.

Elschnig Spots

Elschnig spots of the retina are small, white spots or circular areas of hyperpigmentation surrounded by depigmentation. These spots are areas of serous detachment that resolve slowly because of elevated blood pressure. If the detachment resolves fairly quickly, a small depigmented area remains. If the detachment resolves slowly, hyperpigmented spots occur. The production of Elschnig spots occurs at the level of the pigment epithelium and is exacerbated by renal disease.

Nonrhegmatogenous Retinal Detachment

Nonrhegmatogenous retinal detachment is most often inferiorly located and bilateral. Associated with Elschnig spots, it is a localized serous detachment that looks like a white spot of retinal pigment epithelial necrosis. The resolution of this detachment causes an Elschnig-type atrophic spot or a hyperpigmented area. It is exacerbated by renal failure.

Seigert's Streaks

Seigert's streaks appear as radiating streaks extending from the posterior pole into the periphery at the level of the choroid. These are deep to the retinal epithelium. These occur as a result of occlusion of the choroidal artery leading to necrosis of the choroids. The etiology is atherosclerosis secondary to systemic hypertension. This condition is associated with detachment, and immediate referral for blood pressure control is mandatory. Prompt treatment may allow for healing of the choroidal vascular endothelium.

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CHAPTER 9

Pulmonary Disease

CHAPTER OUTLINE

SYMPTOMOLOGY

The most common symptom of lung disease is dyspnea, or shortness of breath. Acute dyspnea that occurs within hours to days may indicate asthma, infection, pulmonary edema, pneumothorax, or pulmonary embolism. Dyspnea that occurs during a period of days to weeks is most often the result of bronchitis. Chronic shortness of breath that occurs during a period of months to years typically indicates chronic obstructive pulmonary disease (COPD).

Coughing is also a common symptom associated with pulmonary disease, but is not useful in the differential diagnosis because it is so nonspecific. The coughing up of blood, or hemoptysis, is a rare symptom associated with disease of the lung tissue or vasculature. Such disorders include bronchitis, cystic fibrosis, neoplasm, pneumonia, or tuberculosis.

DIAGNOSIS

After the intake interview and a thorough history, the physician will perform a physical examination that includes inspection, palpation, percussion, and auscultation. The inspection qualifies the pattern of breathing and quantifies its rate. Any asymmetry of lung expansion is noted. Other abnormalities that can be isolated during inspection include rapid or labored breathing and dyspnea.

The symmetry of lung expansion can also be evaluated by palpation. Asymmetry may occur because of pleural fluid trapped between the lung and chest wall.

Percussion can further evaluate this condition; pleural effusion will cause a dull sound. Emphysema, or air in the pleural space, causes a sharp percussive sound.

Some abnormal breath sounds include wheezes, rales, and rhonchi. Wheezes occur during expiration and indicate the narrowed bronchial lumen that can occur with airway edema, pulmonary neoplasm, or airway secretions. Rales, or crackles, occur during inspiration, and indicates interstitial lung disease. Rhonchi occur when fluid is present in the lumen of the airway that produces a vibratory sound.

Radiographic analysis of the chest may provide valuable initial information on respiratory disease. X-ray analysis of the lungs may show typical radiographic patterns of disease including a diffuse nodular pattern characteristic of neoplasm or tuberculosis, a diffuse alveolar disease typical of sarcoidosis, a diffuse interstitial disease, or a localized infiltrate indicative of pneumonia. Computed tomography (CT) and magnetic resonance imaging (MRI) may further define respiratory disease.

More specialized lung testing includes pulmonary angiography, needle aspiration for culturing, and bronchoscopy for direct visualization of the bronchial tree.

Laboratory testing may be used to measure the arterial blood gases and determine the presence and amount of hypoxemia (hypoxia), which is a reduction in O_2 saturation of the arterial blood. The laboratory may also be used to collect and culture the sputum sample.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Definition

As a category, the COPDs represent lung disorders characterized by a slow progression of reduced expiration. COPD is an inflammation of the airways and distal airspaces. A COPD with normal lung architecture but permanent enlargement of airspaces is diagnosed as emphysema. A COPD with a productive cough of at least 3 months' duration during a 2-year period is diagnosed as chronic bronchitis.

Etiology

COPD is exacerbated by dust, cigarette smoke, air pollution, toxic gases, pulmonary infections, and reduced antioxidant intake.

Pathophysiology

These environmental stresses, as well as genetic predisposition and influences, cause the epithelium of the airways to undergo squamous metaplasia and hypertrophy of the mucous glands. These changes cause the airways to narrow as mucous plugs obstruct the terminal respiratory units. These small airways are obscured by edema, fibrosis, smooth muscle cell infiltration, and goblet cell hyperplasia.

Symptoms

The primary symptom of COPD is dyspnea, and airway obstruction is always found in both emphysema and chronic bronchitis. This obstruction occurs mostly in the small airways when the patient's workload increases and breathing becomes difficult and labored.

Hypoxemia may result if inspired gases are poorly distributed to the plasma (maldistribution of inspired gases is detected on arterial blood gases). The pulmonary circulation becomes adversely affected. When pulmonary hypertension occurs and results in elevations in cardiac output, changes in circulating biochemicals and hormones (including renin, aldosterone, norepinephrine, and antidiuretic hormone) lead to renal dysfunction.

As COPD advances, cachexia, or weight loss, occurs because of alterations in the levels of specific biochemicals. Skeletal muscle and protein are lost which results in a consequential reduction in strength. As wasting of arm and chest muscles advances, dyspnea is worsened, and this leads to worsening of the hypoxemia.

COPD occurs most commonly among smokers who have smoked for at least two decades. The earliest symptoms usually occur in the fifth decade and start as a productive cough. Within a decade, dyspnea may occur and exercise becomes severely limited.

As the disease advances, periods of marked exacerbations occur that can be life-threatening. These episodes usually occur once yearly and can be triggered by cardiac arrhythmia and lung infections. Advanced COPD is characterized by morning headaches caused by increased CO_2 retention.

Diagnosis

Factors that point to a diagnosis of COPD include a history of chronic smoking, wheezing on forced expiration, increased chest diameter, the finding of emphysema on x-ray, and positive pulmonary function testing.

Treatment

The goals of treatment of COPD includes preservation of the airflow and lung capacity, enhancement of pulmonary function, management of hypoxemia, heart, and kidney complications, prevention of further progression of the disease, and avoidance of episodic exacerbations.

Treatment begins with smoking cessation, which serves to reduce malignancy rates, improve cardiovascular health, and improve airflow. Pharmacotherapy includes the use of bronchodilators that reduce dyspnea and improve exercise tolerance. These medications can

be delivered orally or by inhalation. Pills are easy to take but slow to deliver relief. The inhalers are quick to deliver the medication directly to the airways and reduce systemic absorption, but are difficult to time during inspiration. These medications include the beta 2-adrenergic-agonists (i.e., albuterol, salmeterol, and formoterol), anticholinergics (i.e., tiotropium), and theophylline derivatives. The use of glucocorticoids has not been shown to be as effective in the treatment of COPD when compared with its use in asthma. Inhaled corticosteroids have been shown recently to be advantageous in cases of severe COPD, however. Combinations of inhaled steroid and beta 2-adrenergic-agonists have been shown to be more effective than the beta-agonist alone.

Patients with COPD must often be put on chronic oxygen therapy using a nasal cannula and a canister of compressed gas. This therapy helps to reduce depression, improve exercise tolerance and weight gain, and reverse the cellular hypoxia characteristic of COPD.

Three options for surgical therapy are available for patients with COPD: bullectomy, lung volume reduction surgery (LVRS), and lung transplantation. Bullectomy provides benefit in only a small percentage of patients with COPD.

In end-stage COPD, in which emphysema becomes life threatening, lung transplantation is often considered. Half of all lung transplants performed over the last decade have been for COPD.

ASTHMA

Definition

This group of pulmonary diseases is characterized by narrowing of the airways in response to a variety of stimuli. These episodes manifest as acute dyspnea and coughing, and the diseases typically demonstrate periods of exacerbation relieved by long spells of normal respiration. An asthma attack usually lasts from minutes to hours and can occur on a daily basis. Only rarely does an attack lead to death.

Etiology

Most often caused by an allergy, asthma affects tens of millions of people in the United States. A wide variety of antigens have been identified as instigators of an asthmatic attack. The upper airway may become hyperresponsive after an acute viral attack, exposure to toxic levels of gases (i.e., ozone), exercise, emotional stress, and environmental and air pollution.

Exposure to drugs can also exacerbate an asthma attack. Progressive asthma can occur in adults after the consumption of aspirin. Of significant note to the optometrist, the use of topical beta-adrenergic antagonists in the treatment of glaucoma is associated with exacerbations of asthma. The use of topical beta-blockers, whether alone or in combination with other antiglaucoma agents, should be avoided in all patients with glaucoma. The topical use of a beta-blocking agent has been known to cause asthma attacks in previously undiagnosed patients.

Pathophysiology

Asthma involves a state of subacute and chronic inflammation of the tissues of the airways. It is believed that allergens acting as antigens are inspired and activate inflammatory cells on the airway surface epithelium. The release of cellular inflammatory mediators is triggered, including eosinophils and lymphocytes, which release histamine, bradykinin, leukotrienes, and prostaglandins. This process results in lung edema, increased mucus production, and narrowing of the pulmonary airways.

During an asthma attack, airway resistance increases, as does the work of breathing. Air becomes trapped in the lungs and results in a reduction in arterial blood oxygen. This state of hypoxia is typical during an asthma attack. Severe pulmonary obstruction can result in metabolic acidosis.

Symptoms

An asthma attack is typified by wheezing, shortness of breath, and nonproductive coughing. It is episodic and usually occurs on a daily basis, even in a very mild, subclinical form. Often it is characterized by a state of near panic, as the patient begins to gasp for breath and experiences tightness of the chest. It may last for minutes to hours, and often ends with a productive cough.

Diagnosis

A patient whose dyspnea is relieved by the inhalation of a beta-adrenergic agonist has demonstrated a reversible airway obstruction diagnostic of asthma.

Treatment

The goal of treatment is the prevention of future asthma attacks. To this end, elimination of the stimulating allergen is paramount, but often impossible. Environmental antigens are difficult to identify and often their distribution cannot be adequately controlled. In some cases of cold-induced asthma attacks, the ice skater or skier prone to this condition may have great difficulty in giving up their chosen sport.

Short-term pharmacologic relief is provided by adrenergic stimulants that stimulate beta-adrenergic receptors in the lungs and provide airway dilation by inhibiting smooth muscle contraction. These substances are inhaled to provide maximal bronchodilation with a minimum of systemic absorption.

Theophylline compounds are medium-potency medications used for longer-term bronchodilation. This medication is taken usually once daily before bedtime to prevent nocturnal attacks.

Long-term medications that reduce pulmonary inflammation include the glucocorticoids and mast-cell stabilizers. Inhaled steroids remain a mainstay of chronic asthma treatment. These reduce inflammation but do not dilate the airway. The mast-cell stabilizers act to reduce mast cell degranulation and thus reduce the histamine and bradykinin levels. This serves to improve lung function and reduce symptoms. Nedocromil and cromolyn sodium are two examples of inhaled mast-cell stabilizers.

Prognosis

Few people die from asthma, although the mortality rate from this disease is rising in the inner-city environment. This rise is most likely the result of limited health care in these regions.

Long-term changes in lung function rarely occur in asthma and it is rare to see other serious systemic alterations in physiology as commonly occur in COPD. In most cases, asthma occurs in childhood and stays mild throughout the lifetime of the patient. It rarely worsens and continues to be characterized by exacerbations and remissions. Approximately half of all children who develop asthma do not have any attacks after 10 years. Only approximately 10% of children with asthma worsen with age.

PNEUMONIA

Definition

This group of pulmonary diseases is characterized by infection of the lung tissues.

Etiology

Pneumonia can be caused by various species of bacteria, viruses, chlamydia, fungi, and parasites. Some of the common infective sources of pneumonia include influenza, tuberculosis, and histoplasmosis. The most common cause of pneumonia is the bacteria *Streptococcus pneumoniae.*

Pathophysiology

Infectious particles gain access to the lung through inhalation, dissemination from the heart, direct inoculation by a tracheal tube, or stab wounds to the chest. In most cases, pneumonia is caused by aspiration of organisms that commonly inhabit the lining of the oropharynx. In some cases the individual inhales infectious aerosols that bypass the upper respiratory defense mechanisms. Only one infectious particle need be inhaled and deposited in the alveolus to initiate infection.

Symptoms

Pneumonia usually has an acute onset with a sudden production of a fever and a productive cough. The sputum is usually purulent, and chest pain with dyspnea is often present.

Diagnosis

Radiographic analysis reveals pulmonary infiltrates and, in some cases, pulmonary cavities. The key diagnostic test to detect pneumonia is the sputum evaluation and culture. Lower tract secretions for culturing can be safely and effectively sampled by fiberoptic bronchoscopy. Blood testing with culturing of the sample and serology testing can help elucidate the etiology of the pneumonia.

Treatment

The treatment of pneumonia is directed against the offending organism as isolated from the sputum and blood cultures. Antibiotic resistance, as determined by the culture, plays a major role in determining the appropriate antibiotic for treatment. Antimicrobial therapy is usually begun before the radiographic and sputum analysis is available. Because there is a significant amount of resistance to various antibiotic medications, there is no one drug of choice. Preferred antibiotics for the treatment of bacterial pneumonia include penicillin G, amoxicillin, doxycycline, erythromycin, ciprofloxacin, and gatifloxacin.

CYSTIC FIBROSIS

Epidemiology

Of cystic fibrosis (CF) patients, 93% are diagnosed in childhood. Slightly more than one third of these patients survive to adulthood, and approximately one tenth of the population with CF live to be older than 30 years of age. Of patients, 15% are diagnosed in the first 24 hours of life because of gastrointestinal obstruction. CF occurs in approximately 1 of every 3000 live births in the Caucasian population. CF is less common in the African-American population, occurring in approximately 1 of every 17,000 live births.

Pathophysiology

CF is a multisystem, primarily pediatric disease characterized by chronic airway infection that leads ultimately to permanent abnormal dilation of the bronchi.

Destruction occurs within the walls of the medium-sized airways, and fibrous tissue replaces the normal wall components. Thick, purulent secretions appear in the airways associated with bronchial wall ulcerations. This inflammation and bronchial wall destruction is known as bronchiectasis, and is a significant component of CF. Multisystem disorders associated with CF include urogenital, sweat gland, and intestinal dysfunction, and pancreatic insufficiency.

Etiology

CF is a monogenetic disease caused by an autosomal recessive trait. This genetic mutation occurs on chromosome 7 and causes an improper processing and degradation of an important protein. The absence of this protein at crucial sites on the cell wall yields a state of improper cellular function. This dysfunction causes cells to alter their water and electrolyte transport systems and leads to pulmonary, intestinal, pancreatic, and sweat gland dysfunction.

Symptoms and Signs

The most prominent symptoms are cough and chronic sinusitis. The sputum produced is typically green, viscous, and purulent. Blood is often found in the sputum sample (hemoptysis). Associated signs include weight loss, increased sputum production, and worsening dyspnea. Ultimately, there may be respiratory failure. Associated signs of the multisystem characteristics of CF include lower right quadrant pain with failure to pass food, and late onset of puberty.

Diagnosis

The diagnosis of CF is made primarily on clinical signs and symptoms and the analysis of the chloride ion in sweat. Sputum microbiology reveals characteristic infections associated with CF including *Staphylococcus aureus* and *Haemophilus influenzae*. Chest x-rays may reveal small airway obstruction with hyperinflation. DNA analysis is being performed more frequently but remains challenging because of the high rate of CF mutations.

Therapy

Treatment of CF aims to control pulmonary infections, clear airway secretions, prevent intestinal obstruction, and provide nutritional support for appropriate weight management. Pulmonary complications of CF are managed with respiration exercises that help to preserve lung function. Secretions are often removed by using hypertonic saline aerosols. Mucus clearance is also aided by the use of appropriate pharmaceuticals, such as recombinant human DNAse. Antibiotics are used to mitigate pulmonary infections. Short-term bronchodilation can be achieved with inhaled beta-adrenergic agonists or anticholinergics. Pancreatic enzyme replacement therapy will aid digestion and improve weight gain.

PULMONARY THROMBOEMBOLISM

Pathophysiology

Patients inherit a predisposition to pulmonary thromboembolism (PTE) that initiates the sequence of vessel wall damage, hypercoagulation of blood, and venous stasis. An instigating factor, known as a stressor, precipitates this sequence in genetically prone individuals. Such stressors include trauma, surgery, pregnancy, obesity, and the use of oral contraceptives. Often immobile patients, such as pregnant women on long airplane flights, will be prone to the development of PTE. Genetics plays a role in that patients inherit a predisposition to hypercoagulability. The thrombi in these patients tend to develop in the pelvic vein or veins of the leg. Embolization occurs to the pulmonary arterial circulation. Pulmonary embolism then causes increased pulmonary vascular resistance, impaired gas exchange, bronchoconstriction, and lung edema. Death usually results from right ventricular dysfunction, known as right heart failure. Right ventricular failure causes the interventricular septum bulges into the left ventricle. Left ventricular output falls, leading to a decrease in blood pressure, a compromised coronary artery perfusion, and eventual myocardial ischemia.

Diagnosis

Patients with PTE are seen with significant dyspnea. Lung pain, coughing, and hemoptysis may occur. Large PTEs may provoke syncope, fever, chest pain, cyanosis, and tachycardia. Enzyme-linked immunosorbent assay (ELISA) testing for plasma D-dimer is often positive in PTE. Electrocardiogram results reveal sinus tachycardia. Chest x-rays are typically normal in cases of PTE, but chest CT, lung scanning, echocardiography, and pulmonary angiography are the principal tests to diagnose PTE.

Treatment

The goal of PTE treatment is the dissolving of the clot, pain relief, and the prevention and management of deep vein thrombosis (DVT). Treatment of the primary blood clot consists of thrombolysis with a pharmaceutical agent such as recombinant tissue plasminogen activator (TPA), or removal of the PTE by embolectomy. Long-term management includes the use of anticoagulating agents such as heparin and

warfarin for the treatment of DVT. Nonsteroidal anti-inflammatory agents (NSAIDS) may be helpful for pain relief. Beta-adrenergic agonists may be used to treat right heart failure. Insertion of a vena cava filter may be necessary in cases that do not respond to pharmaceutical intervention.

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CHAPTER 10

Liver Disease

CHAPTER OUTLINE

CHARACTERISTICS OF LIVER DISEASE

In general, liver disease may manifest as one of two distinct clinical entities. The condition may be obstructive, as in cholestatic disease, or hepatocellular. A patient with a liver that is inflamed, injured, or necrotic is considered to have hepatocellular disease. The causes of hepatocellular disease include alcoholism and viral hepatitis. Cholestatic liver disease is characterized by obstruction of bile flow and can be caused by such entities as gallstones, drugs, and neoplasm.

The symptomology will implicate one of these two clinical categories, and the physical examination with laboratory testing will usually pinpoint the diagnosis. Additional testing includes radiographic analysis of the liver and surrounding structures and liver biopsy.

Symptoms

Jaundice

Also known as icterus, jaundice represents an elevated serum bilirubin. Bilirubin is a breakdown product of hemoglobin that is produced in the spleen and liver. The state of hyperbilirubinemia results from a diseased liver that overproduces bilirubin, or from an impairment in the excretion of bilirubin. Elevated bilirubin causes a darkening of the urine. The large quantity of elastin in the sclerae tends to accumulate bilirubin resulting in yellow-appearing eyes, or scleral icterus. Jaundice also causes a yellowish-orange discoloration of the skin that remains the most reliable method of assessing the severity of liver disease.

Pruritus

Acute liver disease typically causes body-wide itching. Pruritus often occurs in association with acute hepatitis, biliary obstruction, and cirrhosis. Although typical in acute conditions, chronic liver disease can also cause itching.

Right Upper Quadrant Pain

Tenderness experienced by the patient when the area over the liver is palpated is a typical presenting symptom in liver disease. Severe right upper quadrant pain occurs in gallbladder disease and acute hepatitis.

Abdominal Distention

Abdominal swelling may be caused by liver disease. Cirrhosis may cause fluid retention within the abdomen known as ascites. The patient with abdominal distention may at first notice an enlarging flank that makes normal fitting clothes difficult to button or fasten.

Fatigue

A feeling of tiredness and a lack of energy is the single most common presenting symptom of liver disease. Unfortunately this symptom is very nonspecific, because so many disorders can cause lethargy. When associated with liver disease, fatigue tends to be worse in the afternoon and after exercise.

Palmar Erythema

Also known as "liver palms," this clinical sign of chronic liver disease is characterized by a red discoloration of the palms of the hands (Figure 10-1).

Spider Angioma

This nevus of the cheek represents dilated vascular lesions under the epidermis that resemble spiders. This condition is the result of chronic liver disease and is most often found associated with hepatic cirrhosis (Figure 10-2).

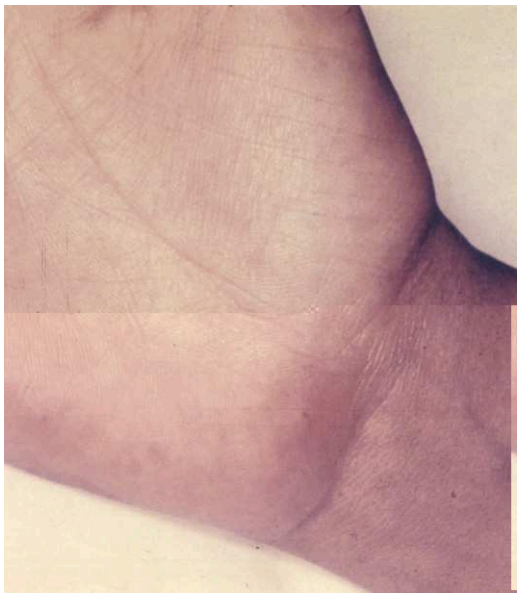

FIGURE 10-1 ■ Palmar erythema ("liver palms"). A clinical sign of chronic liver disease is this red discoloration of the palms. (From Goldman L, Ausiello D: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Elsevier.)

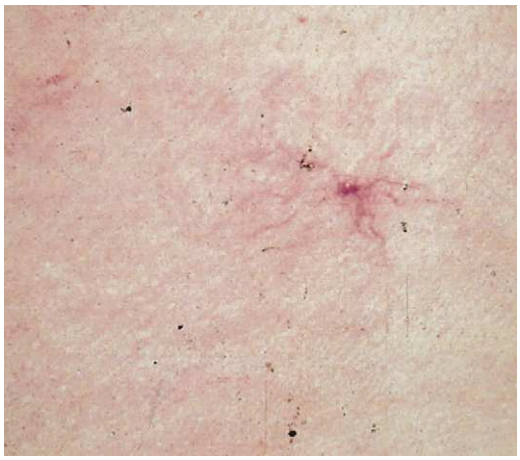

FIGURE 10-2 ■ Spider angioma (cheek nevus). Dilated vascular lesions of the cheek that resemble spiders due to chronic liver disease (hepatic cirrhosis). (From Goldman L, Ausiello D: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Elsevier.)

Evaluation of the Patient with Liver Disease

The majority of patients with liver disease seen in the physician's office are there because of the clinical sign of jaundice. Patients will notice the yellowing of their sclera, particularly if they are contact lens wearers. In addition, many report that friends or relatives notice the yellowing of the patient's eyes.

Body-wide itching is another common clinical sign of liver disease that motivates patients to seek medical care. The itching can be relentless and distracting. It is not as specific a sign of liver disease as jaundice, however, and may occur from such wide-ranging conditions as allergy and pancreatic cancer.

Patients with right upper quadrant pain, or tenderness over the liver, often seek medical help. Often, however, they may delay medical intervention, because this symptom may be interpreted as a stomach virus or muscular cramp.

Because they are such nonspecific symptoms, fatigue and nausea rarely motivate the patient to seek medical help.

Clinical History

The patient should be asked about nausea, fatigue, pain in the right upper quadrant, and body-wide itching. The history should also include the major risk factors for liver disease, including sexual activities, the use of alcohol and intravenous drugs, exposure to jaundiced individuals or needle stick, recent surgeries or blood transfusions, and family history of liver disease.

Physical Examination

The physical examination is oriented towards the detection of icterus, or yellowing of the skin and eyes. Palpation of the right upper quadrant may uncover hepatic pain and tenderness. The optometrist should inspect for scleral icterus under natural light.

Laboratory Testing

Serum testing for liver disease includes serum alanine (ALT) and aspartate aminotransferases (ALT). Other valuable liver serum tests include alkaline phosphatase (AP) and serum bilirubin. In addition, viral serology can help detect and diagnose viral hepatitis.

Imaging

Computed axial tomography (CAT) scan imaging is useful in the evaluation of obstructive jaundice. The hemodynamics of the liver can be evaluated by Doppler ultrasonography and magnetic resonance imaging (MRI). Liver masses can be evaluated by CT and MRI.

Liver Biopsy

Chronic liver disease is best evaluated by liver biopsy. This method allows for the most accurate diagnosis and staging of liver disease possible. The biopsy also helps evaluate the effectiveness of treatment and helps to form the prognostic opinion.

CLASSIFICATION OF LIVER DISEASE

Liver disease can be classified as either hepatocellular or cholestatic. Hepatocellular diseases include viral hepatitis, drug toxicity, alcoholism and chronic cirrhosis. Cholestatic liver conditions include gallstones and malignant obstructions.

Hepatocellular Diseases

Viral Hepatitis

Acute viral hepatitis is caused by a systemic viral infection that affects the liver. Five viruses can cause hepatitis; each has its own characteristics yet all have fairly similar clinical presentations. Symptoms and signs of viral hepatitis range from nonexistent to fulminate and disabling disease. The disease state may be subclinical for the lifetime of the patient, or it can be persistent and complicated and lead to destruction of the liver. Liver destruction occurs because of the immune response of the host and not by direct injury from the hepatovirus. Serologic testing is necessary to determine which virus is causing the liver damage.

Hepatitis A

Caused by an RNA virus, hepatitis A (HAV) incubates for one month and replicates only in the liver. For 2 to 4 months after infection, HAV causes an immunoglobulin M (IgM) antibody response that converts to an immunoglobulin G (IgG) response after 5 months. Acute HAV infection is diagnosed by detection of an IgM response. The IgG response is detectable for the life of the patient. Early on, virus sheds into the feces, and so the fecal-oral route is the primary means of transmission. HAV outbreaks occur in areas of overcrowding and filth. The disease has been linked to poor personal hygiene and the failure of food employees to wash their hands after defecating. Improved sanitation will reduce the incidence of HAV infection. In rare cases HAV has been linked to the consumption of contaminated shellfish. HAV causes a mild presentation and may cause jaundice. The disease is detected early in the infection by an elevated anti-HAV IgM. Almost all patients with HAV infection fully recover with no significant sequelae. Some patients may have a recurrence of the hepatitis months after the initial infection. HAV is not associated with cancer, and the prognosis without treatment is excellent. Liver destruction is almost never seen in HAV infection. Therapy for acute viral hepatitis is limited and not necessary in HAV infection. Immunization against HAV infection is safe and effective for as long as four months. Immunization is often recommended to tourists traveling to areas of poor sanitation, daycare workers, and family members of patients with HAV infection. Vaccination against HAV infection is effective for as long as 20 years and is often recommended to military personnel, daycare workers, laboratory workers, and Alaskan natives.

Hepatitis B

A small DNA virus, hepatitis B (HBV) replicates in the liver but can live elsewhere in the body. These extrahepatic sites include the spleen, lymph nodes, and pancreas. HBV can cause acute or chronic hepatitis and is associated with liver carcinoma. Serologic and virologic markers are detectable after HBV infection to aid diagnosis, prognosis, and help determine length of infection. The HBV virus incubates for 2 to 3 months, and its onset can be either acute or insidious. HBV occurs most often in babies, toddlers, children and young adults. Spread by percutaneous inoculation, fetal delivery, or sexual activity, the HBV disease is occasionally severe. People at highest risk for HBV infection include hospital workers, spouses of HBV-infected individuals and prisoners. Hepatic necrosis is a rare complication of HBV infection. Antiviral therapy is not necessary in cases of HBV because almost all cases of HBV infection recover completely. Vaccination against HBV infection is recommended for hemophiliacs, prisoners, health care workers exposed to blood, intravenous drug users, sexually active individuals, and children younger than 18 years.

Hepatitis C

An RNA virus, hepatitis C (HCV) provokes a cell-mediated response that results in liver injury. It incubates for an average of two months and results in a disease of insidious onset. In the past, HCV infection typically occurred as the result of percutaneous inoculation of contaminated blood, particularly during blood transfusions. Laboratory testing has virtually eliminated this route of transmission. However, HCV is still transmitted through percutaneous injection by IV drug abusers. Exposure to blood products is another route of transmission. The liver disease associated with HCV infection is moderate in presentation and commonly progresses to a chronic state of hepatitis. No known prophylaxis exists against HCV infection, and therapy consists of interferon and lamivudine. A HCV vaccine is still considered impractical, and prevention of HCV involves the alteration of behavior and the appropriate use of precautions against exposure to infected individuals.

Hepatitis D

The RNA virus hepatitis D (HDV) has a one to three month incubation period and causes either acute or insidious-onset liver disease. HDV is spread by close personal contact and exposure to bloodborne products, and is prominent among intravenous drug abusers and certain ethnic populations. HDV infection is often superimposed over HBV infection and can contribute to chronic hepatitis. No treatment exists for HDV infection, and it can be prevented by HBV vaccine. The only therapy for HDV infection is the use of interferon.

Hepatitis E

The RNA virus hepatitis E (HEV) has a 2 week to 2 month incubation period and causes an acute liver disease in the infected, who typically are young adults. The major route of HEV transmission is fecal-oral and results in a mild disease state. Outbreaks throughout the world often occur after major floods because of contamination of the water supply. HEV is rarely spread by person-to-person contact. This virus does not progress to chronic liver disease and it has a good prognosis without treatment. No established prophylaxis or therapy exists for HEV infection.

Hepatovirus Prophylaxis in the Office

The optometrist faced with examining a patient with known viral hepatitis should establish safeguards against contamination. The appropriate use of barrier precautions is essential in preventing spread from the patient to the doctor. Certain challenges prompt the physician to use latex gloves when examining patients who report a positive history of hepatoviral infection. Although it is rare for the optometrist to encounter bodily secretions or blood from the patient, the fingers of the optometrist may be exposed to a significant amount of tears. This mandates the use of latex, or appropriate nonlatex, allergy-free, examination gloves, in all cases of patients with known, active viral hepatitis. The optometrist need not wear gloves in cases of patients with resolved viral hepatitis, unless there is a chronic condition. In this case, and when the patient is unsure whether the condition is resolved, the optometrist should wear gloves. In addition, the optometrist should always wear gloves if any risk of bleeding on the part of the patient exists, even if no known hepatovirus infection is present.

Alcoholic Liver Disease and Cirrhosis

Excessive alcohol consumption is a leading cause of cirrhosis, alcoholic hepatitis, and fatty liver disease. Severe liver disease typically occurs after the patient has consumed approximately five beers per day during a 10-year period. Three beers per day during a 10-year period are enough to produce a fatty liver. Seven beers per day during a 10-year period may result in hepatitis or cirrhosis. Women are more susceptible to developing alcoholic liver disease than men. Patients who test positive for hepatitis C infection are more prone to develop accelerated liver disease.

Fatty Liver

Fatty liver represents the earliest histological response to alcohol-induced injury. In this condition, the liver accumulates fat in the cells responsible for producing an enzyme responsible for alcohol metabolism. Extensive drinking results in further fat accumulation throughout the entire liver lobule. Cessation of drinking allows the liver to regenerate and return to normal, however. Fatty liver is therefore benign and reversible. If the patient continues to drink, a consequential transition from fatty liver to alcoholic hepatitis will occur. Fatty liver is detected on routine physical examination by the discovery of an enlarged liver in a known alcoholic. Rarely, an associated jaundice may be present. Laboratory findings include mild elevations in liver enzyme tests, and elevated cholesterol levels and hyperbilirubinemia. Ultrasound studies of the liver will assess liver size and help in the diagnosis of fatty liver. The treatment of fatty liver disease involves complete cessation of alcohol use. Patient education is necessary to allow the alcoholic to learn about appropriate nutritional alternatives to their previous life style. Psychosocial therapy is mandatory to help the alcoholic through the symptoms of withdrawal. To prevent a relapse, the alcoholic must learn to confront his or her dependency on a daily basis for the rest of his or her life.

Alcoholic Hepatitis

When alcohol-damaged liver cells swell and degenerate, the result is isolated areas of necrosis and fibrosis. Excessive alcohol intake results in a release of cytokines that initiates an immunologic process of liver damage. This state of hepatitis represents a transition from fatty liver to cirrhosis. This form of hepatitis is reversible with cessation of drinking. Clinically, alcoholic hepatitis may be associated with fever, jaundice, and abdominal pain. Laboratory testing reveals significant elevations in liver enzyme levels and significant hyperbilirubinemia. Ultrasound studies can help determine the presence of significant liver disease by detecting ascites, reversal of blood flow in the portal vein, and intra-abdominal collaterals. Mortality rates in cases of severe alcohol hepatitis approach 70%, and these patients often have anemia, low serum protein, and hyperbilirubinemia. Death is often associated with ascites, hemorrhage within the liver, and encephalopathy. Treatment of the hepatitis involves alcohol cessation and the use of glucocorticoids to suppress the immunologic basis of hepatocellular damage.

Alcoholic Cirrhosis

Once the chronic injury to the liver is irreversible a state of cirrhosis is said to exist. Cirrhosis is characterized by fibrosis of the liver, liver cell necrosis and scarring, a loss of liver cells, and a distorted vascular supply. Liver injury induces the deposition of collagen from fibroblasts. Finally, the liver shrinks and becomes hard and nodular. The result is a condition clinically characterized by ascites, jaundice, and encephalopathy. Cirrhosis is often associated with anorexia, weight loss, poor nutritional intake, easy bruising, and fatigue. Alcoholic cirrhosis is the end result of untreated fatty liver and alcoholic hepatitis. This is the most common cause of cirrhosis in North and South America. Laboratory findings in advanced alcoholic cirrhosis include anemia, hyperbilirubinemia, and elevated liver enzymes. No association is known to exist between chronic alcoholism and the development of diabetes mellitus. Cessation of alcohol ingestion may result in a reversal of the cirrhosis. Alcohol counseling is recommended for these patients, because the strict prohibition of alcohol ingestion is necessary to prevent further liver damage. Once liver cirrhosis occurs, aspirin should be avoided, because aspirin metabolism is altered and this in turn affects blood coagulability.

Ocular Evaluation

Chronic alcohol consumption may cause reduced visual acuity in the range of 20/50 to 20/200. Color testing may reveal red-green defects. Visual field testing typically demonstrates central and cecocentral scotomata. The optic nerve heads may appear normal in the early stages of alcohol optic neuropathy, but in the later stages optic nerve swelling may occur with splinter hemorrhages. Eventually, optic atrophy ensues resulting in a pale, atrophic disc. Acute ingestion of alcohol may result in inebriation. An ocular characteristic of the intoxicated patient is endpoint nystagmus on lateral gaze. Commonly, acne rosacea with an associated keratitis results from alcohol consumption (Figure 10-3). Acne rosacea may be treated with either tetracycline, 250 mg four times a day by mouth (prohibited in children), or doxycycline 300 mg three times per day by mouth. With sensitivity to these medications, erythromycin may be substituted at a dosage of 250 mg four times per day by mouth.

Reye's Syndrome. A fatty liver in a child younger than 15 years that results in encephalopathy is known as Reye's syndrome. Although the cause remains unknown, it is postulated that viral pathogens and drugs may be associated with this form of liver disease. One definitive association is the use of aspirin and other salicylates by children. For this reason, the use of aspirin is always prohibited in children younger than 15 years. Symptoms appear soon after the ingestion of aspirin or an upper respiratory condition and include stupor, coma, vomiting, and convulsions. Jaundice is not usually present, but the liver is enlarged and hypoglycemia is typically discovered on laboratory testing. Any child who ingests aspirin accidentally should be taken to an emergency room immediately to watch for signs of Reye's syndrome. Treatment includes infusions of glucose, plasma, and mannitol. Only approximately half of all children with Reye's syndrome survive.

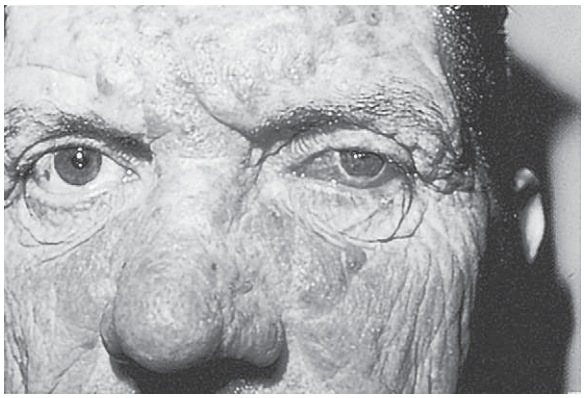

FIGURE 10-3 ■ Acne rosacea. The face shows red papules and pustules and the lids reveal an associated blepharitis. (Courtesy the Department of Dermatology, University of North Carolina at Chapel Hill. From Goldstein BG, Goldstein AO: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

Cholestatic (Obstructive) Diseases

The hallmark of cholestatic disease is an inhibition of bile flow resulting in jaundice. Associated clinical signs and symptoms include itching, fatigue, and right upper quadrant pain.

Gallstone Obstruction

A gallstone is a concretion of bile that consists of cholesterol, calcium bilirubinate, and other salts, protein, and fatty acids. Gallstones form most often among North American Indians and the obese. These obstructions also commonly form in people who are undergoing weight loss programs, women, the elderly, and those eating a high-fat diet. Symptoms are induced by obstruction of the cystic duct and include nausea, vomiting, and severe pain in the right upper quadrant of the abdomen. Stones are diagnosed on radiographic imaging and ultrasound. Treatment involves the use of medication to slowly dissolve the stone during a 6-month period and prevent further stone development (lithogenesis). Some gallbladder stones are amenable to fragmentation by the generation of shock waves. Known as lithotripsy, the use of stone fragmentation negates the use of long-term medication. In cases of severe symptomology, previous gallbladder disease, or very large gallstones, cholecystectomy may

be necessary. Often approached by a laparoscopic method, the gallbladder in this case is entirely removed. Most cases of symptomatic cholelithiasis are now treated by laparoscopic cholecystectomy.

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) appears to be autoimmune in nature, because approximately 90% of patients with this condition have circulating IgG antimitochondrial antibodies. PBC occurs mostly in women. The disease is usually asymptomatic and is detected by an elevation in the alkaline phosphatase level. The earliest symptom is itchiness (pruritus) of the palms and soles of the feet. Jaundice may occur after several months and hyperpigmentation of the skin may be present. As the condition progresses, ascites and hypertension may develop. No effective treatment for PBC exists at this time. The use of ursodiol may increase the lifespan and reduce the symptoms of the patient, but this has yet to be confirmed. The eventual liver destruction mandates a liver transplant and results have been excellent in these cases.

Drug-Induced Hepatitis

Liver injury may result from the ingestion of drugs because of cellular membrane distortion or the blocking of biochemical pathways. Necrosis follows and the bile ducts become injured, and this in turn blocks lipid movement and causes fat accumulation. The effect may be the result of a direct toxic effect on the liver, as in tetracycline-induced hepatitis, or idiosyncratic, as in isoniazid and chlorpromazine-induced hepatitis. Medications known to cause cholestasis include erythromycin, rifampin, oxacillin, methimazole, and cyclosporine.

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CHAPTER 11

Gastrointestinal Disease

CHAPTER OUTLINE

SYMPTOMS OF GASTROINTESTINAL DISEASE

Dysphagia

When a patient has difficulty swallowing, he or she often describes a "sticking" sensation that occurs when food passes through the throat. Often the patient will feel a sensation of a throat obstruction. A complete throat obstruction produces the inability to swallow, or aphagia. Dysphagia may be produced by stroke, toxins, Sjögren's syndrome, myasthenia gravis, tumors of the throat, enlarged thyroid gland, a large-sized bolus of food, or inflammation of the throat structures.

Nausea and Vomiting

Vomiting, or emesis, is the uncontrollable oral expulsion of contents from the upper intestine and stomach. Vomiting is often preceded by nausea and the urge to vomit. Nausea and vomiting are caused by factors that include drugs, surgery, toxins, inflammations, motion sickness, psychiatric disorders, infections and reflux, myocardial infarction (MI), gastrointestinal (GI) obstructions, and intracranial masses and hemorrhage.

Gastrointestinal Reflux Disease

Gastrointestinal reflux disease (GERD) is so common that is has been reported to occur in 40% of Americans at least once monthly. During a bout of GERD, acid refluxed from the stomach bathes the esophagus and causes a burning sensation. In 5% of cases, esophageal ulcers result from the chronic, recurrent exposure to GI acid. The typical symptom of GERD is heartburn, in which a patient feels a substernal warming that extends to the throat.

Diarrhea

More than a billion people worldwide suffer at least one bout of diarrhea per year. Every year 50 million people in the United States must restrict activities because of acute diarrhea. Eight million children die worldwide each year from chronic diarrhea. Diarrhea results in watery, unformed feces passing quickly through the GI

tract. Causes of acute diarrhea lasting less than 2 weeks include infections, Reiter's syndrome, medications, and psychogenic factors. Chronic diarrhea lasting longer than 4 weeks may be caused by medications, surgery, hormonal changes, bacterial infections, lactose intolerance, inflammatory bowel disease (IBD), Crohn's chronic ulcerative colitis, radiation treatment, and psychogenic factors.

Weight Loss

Unintentional weight loss in an otherwise healthy patient may be an early sign of a serious underlying condition. In the elderly, weight loss is often the result of depression, although cancer and IBD should be excluded. Besides cancer, other causes of weight loss include anemia, arthritis, infections, medications, stroke, eating disorders, alcoholism, renal insufficiency, malabsorption syndrome, and emphysema and COPD.

Gastrointestinal Bleeding

Bleeding from the GI tract may occur from the mouth (hematemesis) or the rectum (hematochezia). The blood may be bright red or black. If the bleeding is detected only by laboratory testing it is referred to as occult GI bleeding (GIB). GIB can cause syncope, lightheadedness, and difficulty breathing. The most common cause of an upper GI bleed is ulcer, followed by varices and, in rare cases, malignancy. Lower GI bleeds (LGIB), when intestinal, are most often the result of tumors such as lymphomas and the use of NSAID medications.

ANATOMICAL CORRELATION OF GASTROINTESTINAL SYMPTOMS

Esophagus

Heartburn and dysphagia, or difficulty in swallowing, both often arise from esophageal problems. These conditions are usually investigated with esophagoscopy, the technique of visualizing the esophagus.

Stomach

The symptoms and signs of nausea, vomiting, and epigastric pain often arise from stomach ailments. The stomach is evaluated by an upper GI x-ray series and gastroscopy.

Small Intestine

Pain, nausea, vomiting, and diarrhea are typical symptoms arising from small intestine disorders. This is investigated by techniques such as duodenoscopy, kidney-ureter-bladder x-ray series, CT, stool cultures, and colonoscopy.

Colon

Diarrhea, pain, blood in the feces, and constipation are typical symptoms and signs arising from colon disorders. Such procedures as colonoscopy, sigmoidoscopy, barium enema, and stool culture are used to study the colon.

Anus/Rectum

The anus/rectum produces symptoms including pain, pruritus, constipation, and incontinence. This area is evaluated by sigmoidoscopy.

SIGNIFICANT GASTROINTESTINAL DISEASES

Peptic Ulcer Disease

An ulcer consists of an inflammatory defect in the mucosal wall of the stomach or duodenum. Ulcers produce a chronic excavation of the gastric epithelial mucus lining that causes epigastric pain made worse by fasting and better by eating. The majority of gastric ulcers are associated with *Helicobacter pylori* infection and NSAID use, although malignancy is a possibility. Treatment for peptic ulcer disease (PUD) includes the eradication of *H. pylori* infection and the prevention of NSAID-related ulcer formation. Antacid use also helps to treat acid peptic disease. Surgical approaches exist that are designed to decrease acid production.

Absorption Disorders

Absorption disorders almost invariably cause a reduced absorption of a necessary compound and are therefore often referred to as malabsorption syndromes. The most common symptom of absorption disorders is diarrhea. If dietary fat is not absorbed well, the condition is referred to as steatorrhea. For example, the inability to absorb lipids, which may be the result of pancreatitis, produces weight loss and vitamin deficiency. An example of the malabsorption of carbohydrates is lactose intolerance, in which the disaccharide present in milk cannot be broken down for digestion, producing cramps, diarrhea, intestinal pain, and flatulence.

Whipple's Disease

This multisystem condition is caused by the bacteria *Tropheryma whippelii.* Characteristics of this chronic disease include joint pain, heart problems, weight loss, diarrhea, and steatorrhea. This disorder is suspected in middle-aged Caucasian men with an insidious onset of fever, diarrhea, and abdominal and joint pain. Whipple's disease can cause pericarditis and chronic aortic regurgitation and may lead to congestive heart

failure. Ocular signs include bilateral, posterior uveitis, supranuclear palsy with upgaze paresis, papilledema, and cranial nerve III, IV and VI palsies. It is treated with a prolonged regimen of antibiotics including penicillin or trimethoprim.

Vitamin Deficiency

Malabsorption may cause a deficiency in the fat-soluble vitamins (A, D, E, and K) and the water-soluble B vitamins. Pancreatic, liver, and intestinal disorders (such as Whipple's disease and Crohn's disease [CD]) can all cause malabsorption of vitamins.

Vitamin A

Known as retinol and the chemically related retinoids, vitamin A is essential for normal vision, cell growth and cell differentiation, humoral immunity, and phagocytosis. Approximately 80% of all vitamin A found in the body is absorbed from food, and approximately half of this amount is held in reserve in the liver. The remaining portion of ingested vitamin A is excreted in the urine or bile. The liver intermittently excretes vitamin A in the form of retinol bound to a specific protein. Through a complex chemical reaction, vitamin A then enters the cell to be used as transporting agents and enzyme reaction enablers. These elements function to control cell proliferation and differentiation. In the eyes, a form of vitamin A known as retinaldehyde acts as a visual pigment to help capture light and produces a nerve impulse that causes a visual response.

Dietary sources of vitamin A include eggs, butter, cheese, fish, liver, dark-green leafy vegetables, and dark-colored fruits. Poor sources of vitamin A include mother's milk, cow's milk, rice and wheat. Vitamin A deficiency can lead to blindness and death. Patients with vitamin A deficiency may develop skin lesions, night blindness, dry-eye syndrome (Figure 11-1), and xerosis. White patches of keratinized epithelium may form on the sclera and are known as Bitot's spots. Eventually the cornea may ulcerate, causing perforation and permanent corneal scarring. Xerophthalmia, a condition characterized by the sloughing of the corneal epithelium, prevents corneal wound healing and is aggravated by the dry eye condition. In extreme cases of avitaminosis A, the conjunctiva shrinks and scars, and abnormal adhesions develop on the eyelid. This condition is known as cicatricial pemphigoid and results in adhesions of the palpebral conjunctiva to the bulbar conjunctiva (Figure 11-2).

Vitamin A deficiency may be detected by blood testing of the serum retinol level. Treatment of vitamin A deficiency includes an intramuscular injection of 100,000 units of vitamin A, or 200,000 IU of vitamin A by mouth. This is followed by 200,000 IU of vitamin A orally every 6 months.

In adults, the daily intake of vitamin A should not exceed 10,000 IU. Overdosage of vitamin A can lead to toxicity and result in vertigo, diplopia, seizures, and increased intracranial pressure. Vitamin A toxicity may occur in adults who ingest 50,000 IU of vitamin A on a daily basis for several months. Symptoms include headache, dry skin, vomiting, diarrhea, and lymph node swelling. Optometrists should be aware of the potential of pseudotumor cerebri in vitamin A toxicity, and screen all patients with papilledema for possible vitamin A overdosage.

Vitamin D

Vitamin D is a hormone produced in the skin by exposure to sunlight. Dietary sources of vitamin D are not necessary as long as adequate sunlight reaches the skin. The two forms of vitamin D interact with parathyroid hormone to regulate calcium and phosphate levels in the bone, small intestine, and kidney.

A deficiency of vitamin D causes rickets, wherein there is mineralization of the skeletal matrix. The

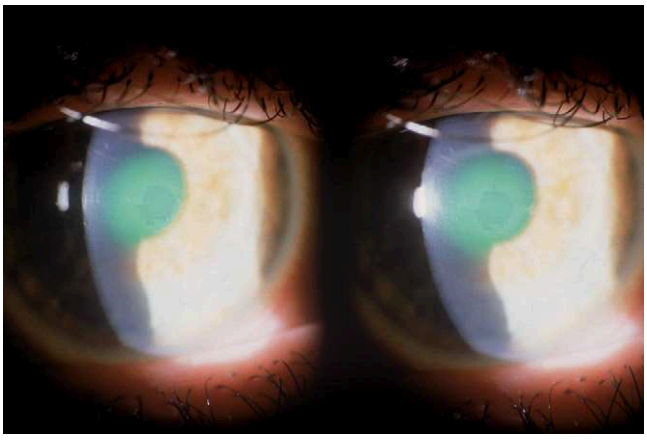

FIGURE 11-1 ■ Dry eye with superficial punctuate staining.

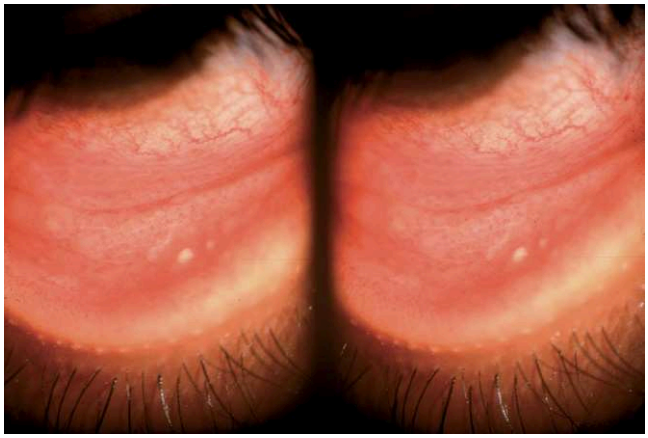

FIGURE 11-2 ■ Symblepharon: Adhesions of the palpebral to the bulbar conjunctiva.

growing bones in children with rickets undergo bowing, stunting, and fractures. Treatment of rickets includes sun exposure, oral vitamin D (800 IU daily for 6 weeks followed by daily 200 IU supplements) and monitoring for bone healing during a 6-month period.

Overdosage of vitamin D may occur with an intake as low as 1800 IU per day. Symptoms of vitamin D toxicity include fatigue, headache, nausea, vomiting, and diarrhea. Areas of calcification may occur throughout the body. Vitamin D toxicity may cause optic atrophy in infants because of hypercalcemia. Calcium deposits in and around the optic foramina create a narrowing of the opening that leads to pressure on the optic nerve. Band keratopathy may be produced in cases of hypervitaminosis D (Figure 11-3).

Vitamin E

Vitamin E is a potent antioxidant radical scavenger and thus protects cellular structures from harmful free radical oxidation. Vitamin E also acts as an antiinflammatory by inhibiting prostaglandin synthesis. Approximately half of the vitamin E that is ingested is absorbed and transported to the liver. In the liver, vitamin E binds to lipoproteins to become widely distributed throughout all tissues in the body. Most of the vitamin E is then stored in muscle and fat, and the remainder is excreted in feces and urine. Dietary sources of vitamin E include meat, nuts, grains, and vegetable oils.

No known deficiency of vitamin E exists, but a toxic dose of greater than 800 mg/d may reduce platelet aggregation and so is contraindicated in patients taking blood-thinning agents.

Vitamin K

The two forms of vitamin K are found in meat and vegetables (vitamin K_1) and synthesized by bacterial flora (vitamin K_2). Vitamin K plays a significant role in blood coagulation and a deficiency results in bleeding problems. High doses of vitamin K can impair the actions of oral anticoagulants and result in blood coagulation and increase the risk of stroke. Vitamin K toxicity may occur if too much is absorbed from a diet high in dark-green leafy vegetables, such as might be prescribed to patients with age-related macular degeneration (ARMD). Therefore ARMD patients placed on blood thinners such as Coumadin should be warned about the risks of eating a diet rich in vitamin A, and limit items such as dark-green leafy vegetables, olive oil, butter, margarine, liver, milk, beef, and coffee. In these cases, the risks of blood clotting because of high levels of vitamin K may outweigh the benefits of stabilizing the macular degeneration condition.

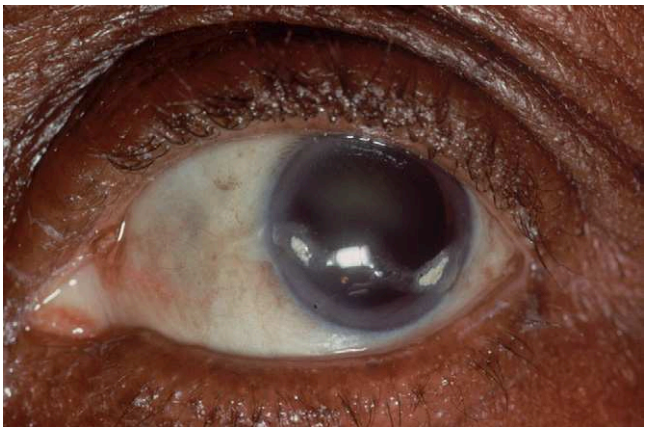

FIGURE 11-3 ■ Band keratopathy. Calcium deposits in the cornea in hypervitaminosis D.

Vitamin B_1

Thiamine is a coenzyme used for cleavage of carbon-carbon bonds. This nutrient also aids in the metabolism of carbohydrates and amino acids. Vitamin B_1 may aid in peripheral nerve conduction. B_1 is stored in the brain, heart, liver, kidneys and muscle tissue. Thiamine is transported through the body bound to plasma proteins and red blood cells. It is found in yeast, pork, beef, grains and nuts. This vitamin is reduced in the body by the consumption of rice, coffee, and tea.

A deficiency of vitamin B_1 results in anorexia, apathy, and weakness. Eventually heart problems may occur, including tachycardia and congestive heart failure, known as beriberi. Wernicke's encephalopathy occurs because of vitamin B_1 deficiency associated with alcoholism, and is characterized by horizontal nystagmus, ophthalmoplegia, and mental impairment. Treatment includes the parenteral or oral delivery of thiamine.

Vitamin B_2

Riboflavin is a cofactor for oxidation reduction reactions. Important in the metabolism of fat, protein, and carbohydrate, vitamin B_2 is primarily found in milk, eggs, fish, and broccoli. Ocular manifestations of vitamin B_2 deficiency include reduced visual acuity secondary to cataract and keratoconjunctivitis sicca with subsequent corneal neovascularization. Angular cheilitis at the corners of the mouth represent infection in the folds of the skin because of vitamin B_2 deficiency (Figure 11-4). Such deficiency may also lead to a loss of papillae on the tongue (Figure 11-5), known as a "smooth tongue."

Vitamin B_3

Niacin is a coenzyme used in oxidation and reduction reactions. Niacin is further used in fatty acid and steroid biosynthesis and glycolysis and protein metabolism.

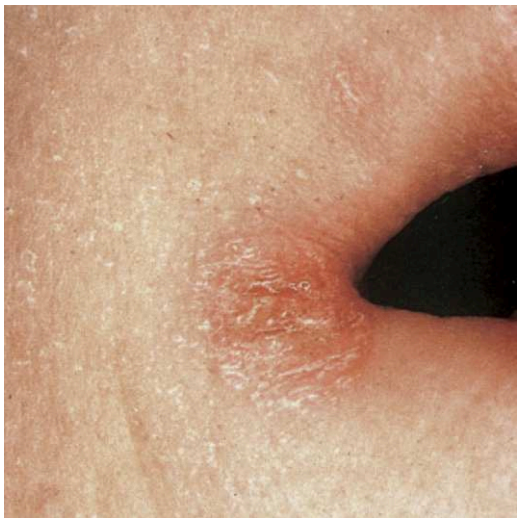

FIGURE 11-4 ■ Angular cheilitis (angular stomatitis). Infected folds of skin at corners of mouth caused by vitamin B_2 deficiency. (From Mandell GE, Bennett JE, Dolin R: *Principles and practice of infectious diseases,* ed 6, Edinburgh, 2005, Churchill Livingstone.)

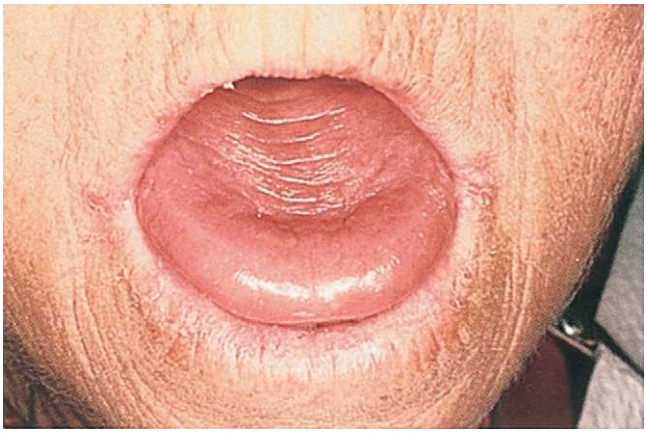

FIGURE 11-5 ■ Smooth tongue. This smooth, red, glossy appearance is caused by loss of papillae from anemias, vitamin deficiency, and malabsorption syndromes. (From Feldman M: *Sleisenger & Fordtran's gastrointestinal and liver disease,* ed 8, Philadelphia, 2006, Saunders.)

Niacin deficiency produces pellagra. This condition begins with a loss of appetite, weakness, stomach pain, and vomiting, and proceeds to skin rashes, diarrhea, depression, seizures, dementia, and death.

Niacin is used to treat hyperlipoproteinemias and acts to decrease blood cholesterol. In therapeutic doses, vitamin B_3 may cause a classic "flushing" of the skin, a temporary reddening of the face.

Vitamin B_5

Pantothenic acid is a cofactor in energy metabolism, steroid hormone synthesis, and hemoglobin formation. This nutrient is found primarily in beef, cereal grains, and dark-green leafy vegetables.

Vitamin B_6

Pyridoxine is a cofactor for enzymes of amino acid metabolism, and is also involved in neurotransmitter synthesis. It is found in meat, nuts, and wheat bran. A deficiency may occur in patients taking isoniazid, oral contraceptives, L-dopa, and some antibiotics, and results in weakness, dermatitis, depression, confusion, and peripheral neuropathy.

Vitamin B_9

Folic acid has been shown to prevent disease and its prenatal supplementation prevents neural tube disorders. Found in nuts, fruit, liver, lentils, and leafy green vegetables, vitamin B_9 has been suggested as a supplement in a "heart healthy" diet.

Vitamin B_{12}

Primary nutritional sources for this vitamin include meat, fish, liver, and kidneys. A deficiency of vitamin B_{12} results in anemia and neurologic signs.

Biotin

Biotin is a water-soluble vitamin that plays a role in gluconeogenesis and fatty acid synthesis. It also aids in the catabolism of amino acids such as leucine. It is found in liver, soy, beans, yeast, and egg yolks. A deficiency of biotin may result in mental changes including hallucinations and depression. A rash may appear around the eyes with such a deficiency, and treatment consists of oral doses of biotin.

Vitamin C

Vitamin C participates in oxidation and reduction reactions and is a potent antioxidant. Vitamin C is important in connective tissue metabolism and drug-metabolizing tissue enzyme systems. This nutrient is biologically active in the synthesis of corticosteroids and the metabolism of cholesterol.

Vitamin C is found in citrus fruits, green vegetables, tomatoes, and potatoes. A deficiency of vitamin C produces scurvy, a condition characterized by joint pain, weakness, depression, bleeding of the skin and gums, and impaired bone growth in children. Avitaminosis C may yield hemorrhagic conjunctivitis (Figure 11-6). Treatment for scurvy includes vitamin C supplementation.

High-dose vitamin C supplementation has been shown to improve glycemic metabolism. Toxic levels of vitamin C (more than 2 g/day) may produce diarrhea and abdominal cramping.

Inflammatory Bowel Disease

This idiopathic and chronic intestinal inflammation is composed of ulcerative colitis (UC) and CD. IBD is found predominantly in the United States, England,

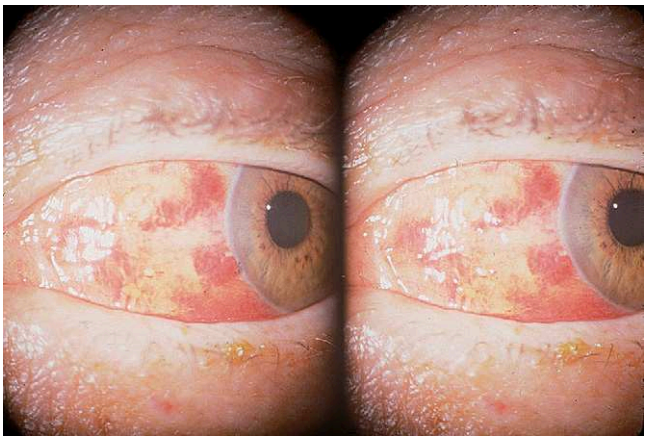

FIGURE 11-6 ■ Hemorrhagic conjunctivitis in vitamin C deficiency.

Norway, and Sweden. The disease occurs primarily in patients between 15 and 30 years. A slightly lower peak occurs in patients between 60 and 80 years of age.

Although the etiology of IBD is as yet unknown, it is hypothesized that in genetically predisposed individuals, infections, smoking, and a host of anatomical factors conspire to cause a chronic activation of the mucosal immune system. IBD appears to be an inappropriate response to these various stimuli. The immune inflammatory response in IBD is perpetuated by T-cell activation. Then, a cascade of inflammatory mediators acts to prolong the response and produces a chronic condition. This inflammatory response results in characteristic small ulcerations and erythema of the colon (Figure 11-7).

Skin findings in IBD include erythema nodosum (Figure 11-8) and pyoderma gangrenosum (Figure 11-9).

Between 1% and 10% of patients with IBD have an associated ocular condition. The most common are conjunctivitis, anterior uveitis, and episcleritis (Figure 11-10). Anterior uveitis is particularly associated with CD, and can produce pain, photophobia, and blurred vision, but can also produce a "silent" uveitis found only on slit-lamp evaluation. Prompt treatment with topical cycloplegic and corticosteroid preparations minimizes scar-tissue formation in these cases of IBD-related anterior uveitis.

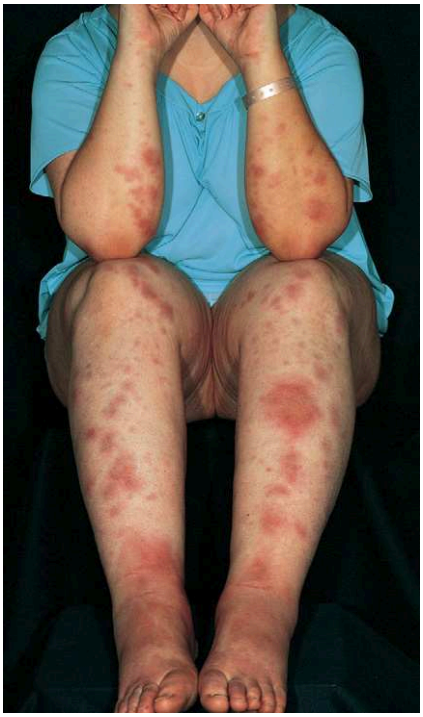

FIGURE 11-8 ■ Erythema nodosum. Bright, red, raised, tender lesions, usually in the front of the shins. (From Habif TB: *Clinical dermatology: a color guide to diagnosis and therapy*, ed 4, St. Louis, 2004, Mosby.)

Ulcerative Colitis

UC is a form of IBD that causes the mucosa of the rectum and colon to become granular, hemorrhagic, edematous, and ulcerated. This process can produce polyps when the epithelium regenerates. A chronic state of UC produces a colon that is atrophic, narrowed, thin, and ulcerated to the point of perforation. Symptoms of UC include diarrhea, rectal bleeding,

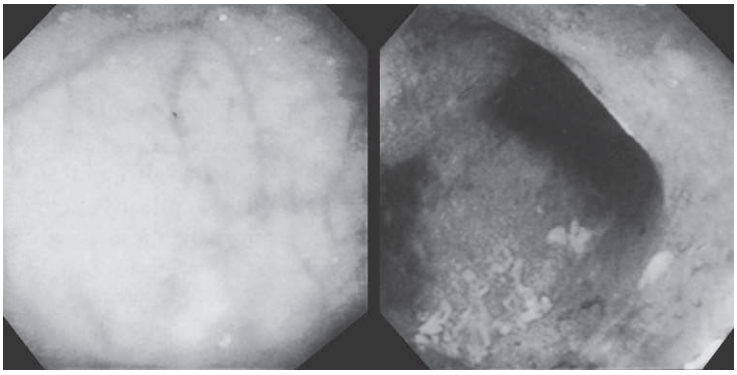

FIGURE 11-7 ■ Normal-appearing colon with vascular integrity preserved *(left)* and the inflamed colon of a patient with inflammatory bowel disease revealing a loss of normal vascular pattern along with small ulcerations and erythema *(right)*. (Courtesy Philip Gilman, MD).

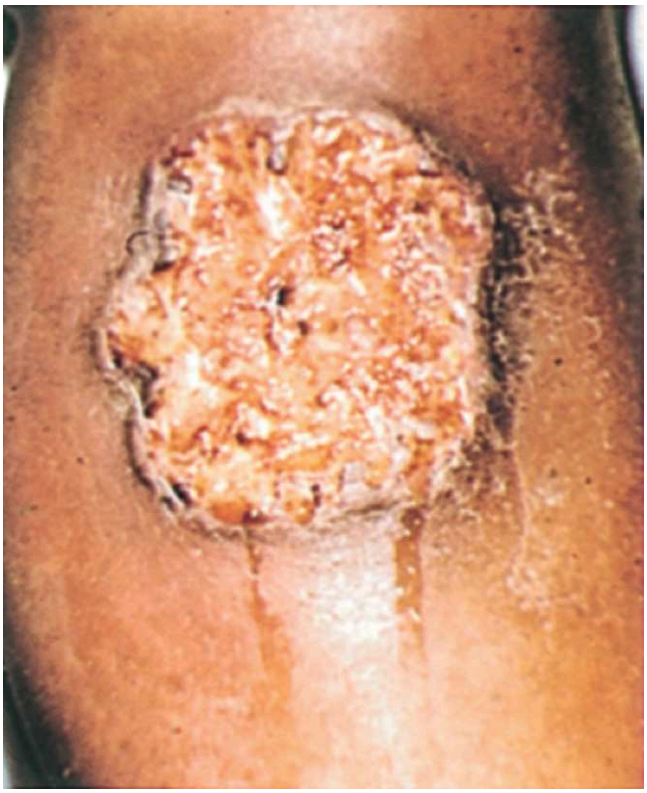

FIGURE 11-9 ■ Pyoderma gangrenosum. An advancing crusted edge with irregular exudative ulceration and central healing with scarring, that is associated with ulcerative colitis. (From Feldman M: *Sleisenger & Fordtran's gastrointestinal and liver disease*, ed 8, Philadelphia, 2006, Saunders.)

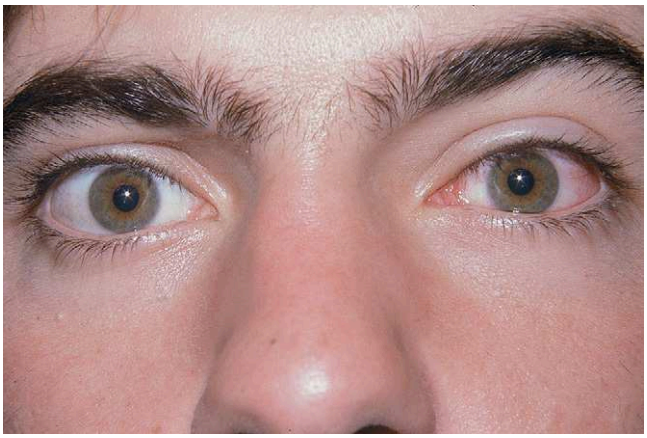

FIGURE 11-10 ■ Episcleritis associated with Crohn's disease.

and abdominal pain. Bleeding may occur mixed with the stool. Laboratory testing reveals an elevated C-reactive protein and erythrocyte sedimentation rate (ESR). Sigmoidoscopy may be used to assess the state of the disease. A barium enema is helpful in making the diagnosis of UC.

Mild-to-moderate UC is treated with sulfasalazine and other 5-ASA agents. These agents deliver antibiotic and antiinflammatory therapy to the colon. Side effects of sulfasalazine are common, and include headache, anorexia, nausea, vomiting, and skin rash. Sulfa-free aminosalicylate preparations have been developed to reduce these unwanted side effects.

Moderate-to-severe UC is treated with glucocorticoids. These steroid preparations should be tapered as symptoms reduce. During periods of remission, steroids should not be used for maintenance therapy.

Antibiotics have not been shown to be effective in the treatment of UC.

Azathioprine is a purine analogue used in conjunction with glucocorticoids for the treatment of UC.

Crohn's Disease

CD can affect all parts of the GI tract, from the mouth to the rectum. CD results in segmental inflammation with associated fistulas, fissures, abscesses, and ulcerations that penetrate deep into the mucus tissue. Resolution of these inflamed areas produces fibrosis and scarring of the bowel. Chronic, recurrent bowel obstructions result from this structuring of the bowel. CD is a granulomatous disease that results in noncaseating granulomas in all layers of the bowel wall, lymph nodes, liver and pancreas.

The symptoms and signs of CD include fever, diarrhea, a palpable mass, and right lower quadrant pain.

Laboratory testing may help differentiate CD from UC.

Mild-to-moderate CD is treated with 5-ASA, metronidazole, or ciprofloxacin, oral glucocorticoids, or azathioprine. Cyclosporin has a role in the treatment of severe CD. Maintenance therapy for CD includes methotrexate (MTX) to prevent exacerbation of the CD.

Anterior uveitis is associated with CD. Patients with CD must be monitored for uveitis at least twice yearly with a slit-lamp examination. Most commonly, the diagnosis of CD-related anterior uveitis is made in the optometrist's office when cells are detected in the anterior chamber of a patient with known CD or with abdominal cramps. The uveitis may occur during periods of quiescence, although patients may notice red eyes associated with bouts of diarrhea and vomiting associated with CD exacerbations.

Behçet's Disease

Behçet's disease, an uncommon, multisystem nongranulomatous disease of unknown etiology, is characterized by GI symptoms, colitis, nonulcerative skin lesions, and uveitis. Its highest incidence is in the Far and Middle East.

Behçet's disease presents as a triad of oral ulcers (Figure 11-11), genital ulcers (Figure 11-12), and ocular

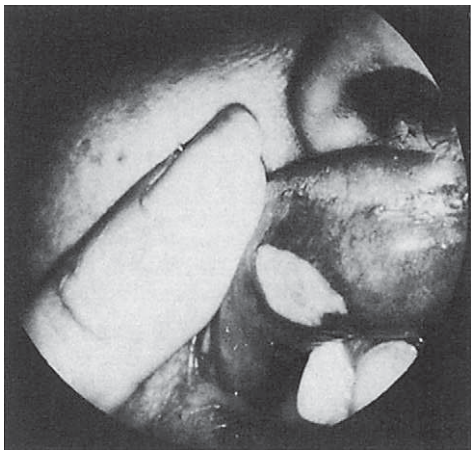

FIGURE 11-11. ■ Oral ulcerations associated with Behçet's syndrome. The condition presents with painful ulcers in the mouth and pharynx. (From Blodi FC: Ocular involvement in dermatologic disease. In Mausolf FA, ed: *The eye and systemic disease*, St. Louis, 1975, Mosby-Year Book.)

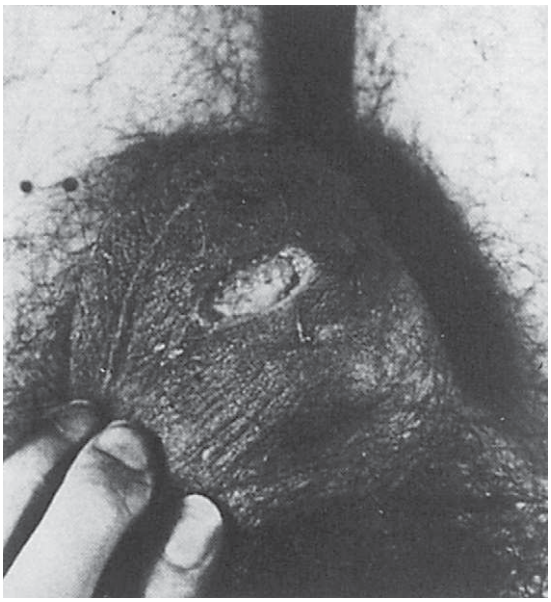

FIGURE 11-12 ■ Genital ulcerations associated with Behçet's syndrome. Recurrent orogenital ulceration. (From Blodi FC: Ocular involvement in dermatologic disease. In Mausolf FA, ed: *The eye and systemic disease*, St. Louis, 1975, Mosby-Year Book).

inflammation. Much of the GI tract may become involved and even the joints may become inflamed. Treatment of Behçet's disease includes systemic corticosteroids and azathioprine.

Ocular sequelae include hypopyon (Figure 11-13), uveitis (Figure 11-14), retinal vasculitis (Figure 11-15), cataract formation, and glaucoma.

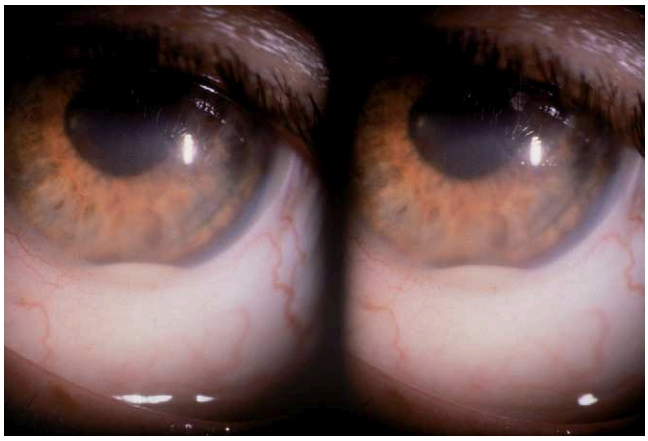

FIGURE 11-13 ■ Hypopyon in a case of Behçet's syndrome.

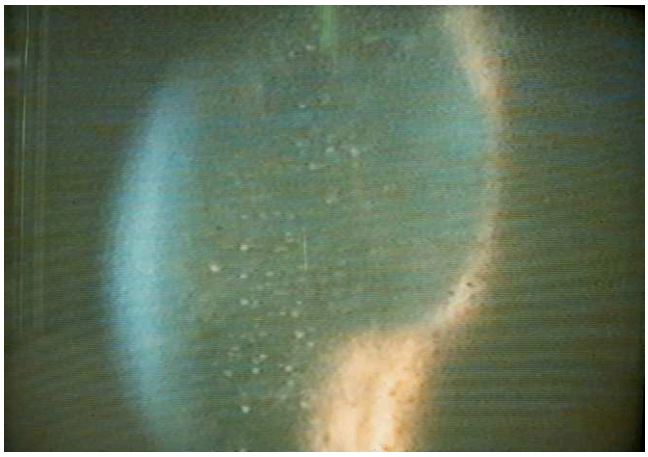

FIGURE 11-14 ■ Cells in the anterior chamber in Behçet's syndrome.

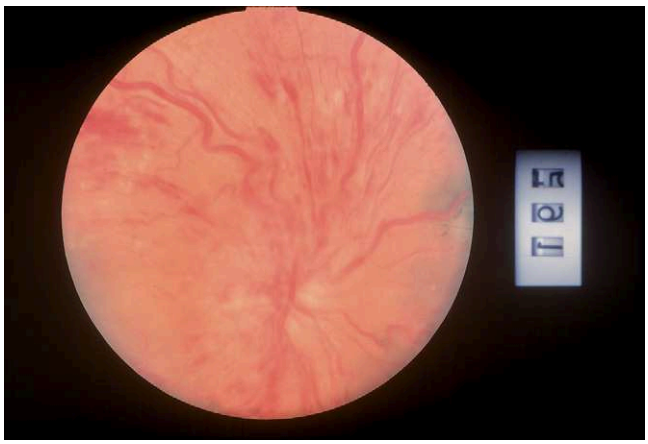

FIGURE 11-15 ■ Central retinal vein occlusion in a case of Behçet's syndrome.

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CHAPTER 12

Endocrine Disorders

CHAPTER OUTLINE

Endocrinology encompasses the action and secretion of hormones, the endocrine glands that produce these chemical messengers, and the regulation of physiological functions by means of feedback mechanisms.

The anatomical basis of endocrinology is the multitude of glands dispersed throughout the body. This chapter discusses specific endocrine glands, including the thyroid gland, parathyroid glands, pituitary gland, adrenal cortex and pancreatic islets, and how derangements in their hormonal secretions cause physiological changes that ultimately affect the visual system.

Endocrine glands release hormones that regulate physiological processes throughout the body. Hormones produce a wide range of effects, including the control of blood pressure and vascular tone, the stimulation for blood production in the bone marrow and growth, the regulation of digestion and serum glucose, and a vast array of other biological functions. The brain itself controls the level of hormonal activity by release of its own hormones, and elegant feedback regulatory systems exist to maintain hormonal balance.

THE ROLE OF HORMONES

A hormone is a chemical produced and secreted by a gland that acts to set in motion cellular responses and physiological processes. Hormones may be synthesized and then stored within granules under the plasma membrane of the gland. A stimulus, such as a neural signal or chemical-releasing factor, influences the secretory granule to merge with the plasma membrane, degranulate, and spill its hormonal contents into the bloodstream. Other hormones, such as steroids, may be synthesized and released directly into the bloodstream.

The level of a given hormone in the bloodstream is influenced by the half-life of the hormone and the rate of its secretion. In addition, most hormones circulate bound to blood proteins. By binding to a certain hormone, a serum protein prevents access to specific sites. In addition, protein binding extends hormonal influence by "pooling" the hormone, effectively increasing the hormone's half-life.

Hormones gain access to specific organs by an interaction with a receptor site. The sites for hormone binding may be nuclear or on the cell membrane. Small molecular hormones such as thyrotropin-releasing hormone (TRH) bind to nuclear sites because they can diffuse across the cell membrane. Large proteins such as insulin bind to cell membrane receptor sites.

Once bound to a receptor site on a cell, the hormone acts to initiate specific biological responses. In most cases, these processes include reproduction, body growth, and maintenance of metabolism and homeostasis.

The maintenance of homeostasis is an impressive example of hormonal influence. All hormones impact

homeostasis, and all positive effects must be balanced with negative feedback to maintain homeostasis. One example of homeostasis is the insulin-glucagon feedback mechanism that maintains a euglycemic state whether the organism is starved or well-fed. Another example is thyroid hormone, which controls basal metabolism in almost all tissues.

In cases of shock, hormones called catecholamines are released under sympathetic nervous control and these chemical mediators increase cardiac output and blood pressure and stimulate glucose production. The result is a stimulated musculoskeletal system ready to confront the stressing agent.

Once an appropriate biological response has been generated, continued hormonal influence may actually be detrimental to the organism. Efficient hormonal feedback regulatory systems have evolved to exert both positive and negative control on endocrine systems.

CAUSES OF ENDOCRINE DYSFUNCTION

Endocrine dysfunction can be caused by tumors, surgery, autoimmune reactions, and inflammatory or infectious processes that affect an endocrine gland. Rarer causes of dysfunction include developmental conditions, infarction of the gland, and nutritional deficiencies.

In general, hormone dysfunction may take three forms: overproduction of the hormone, underproduction of the hormone, or normal hormonal levels with reduced physiological response due to hormone resistance. Excessive hormone production occurs in tumors of the thyroid and pituitary gland. In addition, an autoimmune reaction of the thyroid gland increases hormonal production, causing Graves' disease.

Hypofunctional hormone levels may be the result of autoimmune reactions in such conditions as diabetes, hypothyroidism, and Addison's disease, and inflammatory conditions such as sarcoidosis of the hypothalamus.

DIABETES MELLITUS

Introduction to Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia, or elevated serum glucose. Several forms of DM exist, and are differentiated by the etiology of the hyperglycemia.

Serum blood glucose is maintained, in part, by the action of insulin. This hormone is the most important regulator of glucose use and supply, although several other pathways contribute to glucose homeostasis. Elevated blood sugar may be caused by an increase in glucose production, a decrease in serum glucose uptake by the cells, or a reduction in insulin production. Approximately 18 million people in the United States have DM, and 5 million do not know that they have the disease. Of all diabetics, 95% have type 2 diabetes, and only 5% have type 1 diabetes.

Insulin Characteristics

An amino acid polypeptide, insulin is generated in the beta cells of the pancreatic islets. Its production is influenced primarily by serum glucose. Blood sugar levels exceeding 70 mg/dl stimulate insulin production.

Insulin Production

Glucose is transported into the pancreatic beta cell and, by a series of islet transcription factors (such as the enzyme glucokinase), is converted into pyruvate. The mitochondria of the cell modify pyruvate to produce ATP, which causes the cell membrane to depolarize. When the beta cell membrane depolarizes, calcium channels open and allow an influx of calcium into the cell. Calcium ions stimulate the release of secretory granules that contain insulin.

Effect of Insulin

Once insulin is released into the bloodstream through the portal vein it binds with receptor sites on cells of target organs. Binding of insulin to receptor sites induces the insulin signal transduction pathway, wherein cellular proteins initiate the metabolic actions of insulin. By this pathway insulin ultimately increases glucose uptake by skeletal muscle and fat, and stimulates protein synthesis and lipogenesis.

Glucose Homeostasis

The precise balance of sugar production by the liver (which raises serum glucose) and the uptake of glucose by muscle and fat (which lowers serum glucose) is known as glucose homeostasis. Several factors influence this glucose homeostasis, the most important being insulin. Other regulators of the serum glucose level include metabolic signals, neural input, and hormones such as glucagon.

Glucagon

Glucagon is a hormone that acts counter to insulin, reducing cellular uptake of glucose, thus raising blood sugar.

Glucose Metabolism

When a large amount of food is ingested, the liver will produce a large load of glucose that enters the bloodstream and stimulates insulin production. In addition, the level of glucagons falls. These hormonal shifts cause sugar to enter the cell from the bloodstream and serum glucose to drop. As glucose is used by the skeletal muscle for energy, the fasting state in between meals causes the level of insulin to drop and the level of glucagon to rise to preserve some serum glucose. In

addition, a low level of insulin promotes gluconeogenesis by the liver and raises blood glucose, preventing the state of low serum glucose, or hypoglycemia. If insulin levels remain low, uptake of serum glucose is reduced and this stimulates the mobilization of stored fat for energy. Although skeletal muscle and fat require insulin for glucose uptake, the brain and some other tissues use glucose independent of insulin.

The Pathophysiology of Diabetes

A derangement of one or more of the pathways that control glucose homeostasis causes DM. Obviously, if insulin production is reduced, then glucose cannot enter the cell for use as energy. Another possible mechanism is the inability for the cell to efficiently use the glucose molecule despite a normal amount of insulin. A third cause of diabetes is an overproduction of sugar by the liver. In all three of these cases the disease of diabetes is reflected in a rise in serum glucose. Sustained elevated blood sugar above normal, or hyperglycemia, is considered to be diabetes.

Causes of Diabetes

A destruction of pancreatic beta cells would lead to a loss of insulin and an inability for blood sugar to enter peripheral muscle and fat cells. Such destruction of beta cells occurs by autoimmune processes in genetically susceptible individuals, usually children. The autoimmune process may be triggered by an environmental or infectious (viral) source. At least 80% of beta cells must be destroyed before DM is manifested.

Type 1 Diabetes Mellitus

The nearly complete loss of insulin-producing beta cells causes a rise in serum glucose, reflecting the condition of type 1 DM. In the past this condition was known as insulin-dependent DM (IDDM) as classified by the National Diabetes Data Group of 1979. In 1995 the American Diabetes Association dropped the abbreviated designation "IDDM" while maintaining the term "type 1 DM." One significant reason for this change in designation is that other forms of DM may require insulin supplementation.

Type 1 DM Risk Factors

The patient with Type 1 DM is typically lean, younger than 30 years of age, requires insulin, and often develops ketoacidosis and autoimmune disease.

Type 2 Diabetes Mellitus

Patients with hyperglycemia may not have a complete loss of beta cells but instead may not be able to process glucose because of insulin resistance or lowered insulin production. The cause is as yet unknown, although a genetic predisposition appears to exist stimulated by an as yet unknown environmental factor. This form of DM is known as type 2 DM and may be caused by genetic defects influencing the pancreatic beta cell. Other causes of type 2 DM include drugs, infections, and diseases of the pancreas and other endocrine glands. Whatever the cause, type 2 DM is characterized by an increase in glucose production by the liver, insulin resistance, and decreased insulin production.

Type 2 DM Risk Factors

This form of DM is more common in obese individuals whose parents or siblings have type 2 DM. An increasing risk of type 2 DM in individuals older than 45 years is associated with aging. In addition, African-Americans, Hispanics, and Native-Americans are diagnosed with type 2 DM at a higher rate than other ethnicities. Elevated blood pressure and cholesterol are also factors related to an increased risk of type 2 DM.

Syndrome "X"

The presence of type 2 DM in a middle-aged obese male with high blood pressure and cholesterol places this individual at significant risk for a major vascular event, and is known as "syndrome X." Mental depression often exists as part of this constellation of signs and symptoms. The condition appears to be, in part, the result of a genetic proclivity towards obesity, high blood sugar, systemic hypertension, and elevated cholesterol. Treatment includes weight loss, exercise, appropriate dietary changes, and medical control of the diabetes, blood pressure, and cholesterol. Mental health counseling should be considered in individuals with syndrome "X" who are experiencing any of the symptoms of depression.

Pathophysiology of Type 1 DM

Characterized by hyperglycemia and found often in children, the insulin deficiency in type 1A DM is the result of an autoimmune destruction of beta cells. In type 1B DM, no evidence exists of an autoimmune process and the cause of beta cell destruction is idiopathic.

Pathophysiology of Type 2 DM

More common in obese adults older than 45 years, type 2 DM is characterized by increased glucose production by the liver, impaired insulin secretion from the beta cells, and insulin resistance on the cell membrane. These patients, who usually do not require insulin when first diagnosed, may eventually have elevated serum glucose that remains unresponsive to oral medications. These patients will have type 2 DM that requires insulin.

Diagnosis of DM

There are two criteria to establish a diagnosis of DM. One is the level above which serum glucose produces pathological changes because of hyperglycemia. The

second criteria establishes symptoms or the existence of diabetes-specific complications in a patient.

Glucose tolerance is based on a fasting plasma glucose (FPG) level. Normal FPG is established when a blood sugar level is below 110 mg/dl. An increased fasting plasma glucose (IFG) is found between 110 mg/dl and 125 mg/dl. Patients who exhibit an IFG are at substantial risk for developing DM. DM is diagnosed when the FPG is 126 mg/dl or above in an asymptomatic patient. This result should be repeated on different days for confirmation of the diagnosis.

Acute Symptoms of DM

Most patients with acute hyperglycemia are asymptomatic. When symptoms are present, the three most common are polydipsia (increased thirst), polyuria (increased urination), and polyphagia (increased hunger).

Significant and acute shifts in refractive error occur in patients with rapidly rising serum glucose. For this reason, all ophthalmic patients who demonstrate a large refractive shift should be asked whether any recent increases in hunger, thirst, or urination have been experienced.

In addition, these patients may exhibit a fourth common symptom of acute hyperglycemia; peripheral neuropathy. These patients often seek medical care for hand, wrist, feet, or ankle pain.

Other symptoms of DM include nausea, vomiting, shortness of breath, and altered mental function. These short-term symptoms are most commonly the result of diabetic ketoacidosis.

Diabetic Ketoacidosis

Poorly controlled type 1 or type 2 diabetes may lead to a condition caused by a relative or absolute deficiency of insulin known as diabetic ketoacidosis (DKA). This acute and often life-threatening condition is also characterized by a dramatic increase in the insulin counterhormones glucagon, epinephrine, growth hormone, and cortisol. The principal cause of DKA is the imbalance between insulin and its counterregulatory hormones. The insulin deficiency leads to overproduction of glucose by the liver and an underuse of glucose by the peripheral muscle and fat cells. The liver begins to convert free fatty acids into ketoacids in a pathway known as ketoacidosis. Glucose and ketoacids are both overproduced and underused, leading to hyperglycemia, ketosis, and a loss of potassium. Hyperglycemia causes water to shift out of the intracellular compartment, leading to increased glomerular filtration, osmotic diuresis and urination. Any diabetic patient who goes into shock, coma, dehydration, or cardiac problems should be suspected of having DKA. Laboratory testing will confirm DKA as the lab results usually reveal serum glucose readings of 500 to 600 mg per deciliter and a patient in metabolic acidosis. Therapy of DKA involves appropriate use of insulin, correction of fluid deficits, and replacement of potassium.

Chronic Complications of DM

The long-term effects on tissues in DM may be the result of poor glucose homeostasis, or a toxic effect of hyperglycemia on tissues, although the mechanism of such toxicity has yet to be established. It is unclear how hyperglycemia causes chronic tissue damage, although it is hypothesized that a chronic state of high blood sugar produces damaging compounds that have deleterious biological effects. The chronic complications of DM can be microvascular (eye and nerve effects), macrovascular (carotid artery, peripheral vascular disease [Figure 12-1] and cardiovascular disease), or nonvascular (sexual dysfunction and skin changes).

Targeted end-organ damage in diabetes includes the kidneys (renal disease) (Figure 12-2), nerves (neuropathy), gastrointestinal (upset stomach), heart (congestive heart failure, coronary artery disease, and myocardial infarction), eyes (retinopathy), and an increased risk of systemic infections.

Acute complications can occur at any stage of DM because of a sudden, uncontrolled rise in serum glucose. Chronic complications usually arise after 10 years of DM.

Therapy for DM

For both type 1 and 2 DM the management objectives include the prevention of acute complications and symptoms, the prevention of microvascular and macrovascular complications, the forestalling of atherosclerotic changes, and the achieving of a normal lifestyle.

The patient with type 1 DM must be educated as to the importance of proper nutrition, the balancing of caloric intake with the appropriate amount of insulin, the recognition of plummeting blood sugars, and the

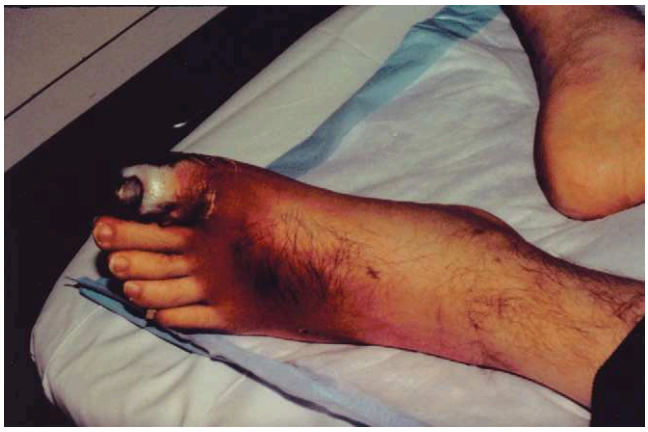

FIGURE 12-1 ■ Gangrenous toe. Gangrene of the toe with cellulitis in a diabetic patient. (From Marx J, Hockberger R, Walls R: *Rosen's emergency medicine: concepts and clinical practice, ed 6,* St Louis, 2006, Mosby.)

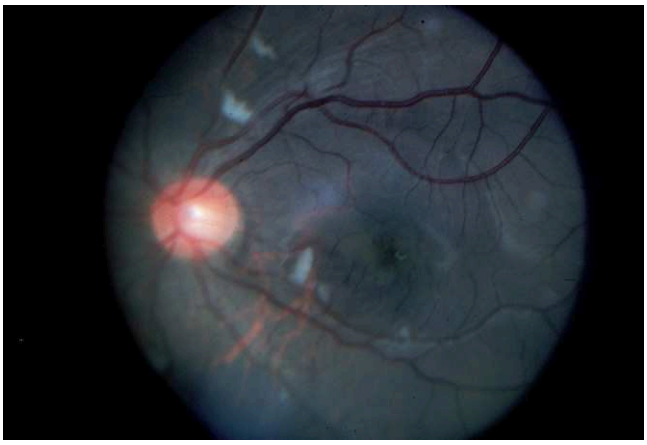

FIGURE 12-2 ■ Kimmelstiel-Wilson retinopathy. This 63-year-old diabetic patient had advanced renal disease with hypertension. Exacerbations in the severity of retinal microinfarction and vascular tortuosity were not associated with chronic capillary closure, but they did correlate with progressive renal impairment.

monitoring of serum glucose. Because these patients are often children, diligence and understanding must be exercised during instruction to achieve the best possible understanding of the seriousness of the condition. Exercise may modulate insulin requirements in type 1 diabetics by maximizing the general health and well-being of the patient while minimizing the risks of hypoglycemia and diabetic complications. In type 1 diabetics, exercise is not expected to improve glycemic control to any great degree. Exercise helps reduce the plasma lipid profile and blood pressure while improving cardiovascular health, however. In general, exercise has been shown to have no effect on glycemic control as assessed by the HbA1c concentrations, but it does lower the necessary insulin dosage by enhancing insulin sensitivity.

The patient with type 2 DM must be similarly instructed on the causes of diabetes, the possible long-term complications, the role of diet and exercise, and the need to monitor serum glucose. All patients with type 2 DM should be placed on an exercise program. In type 2 diabetes, exercise reduces glucose intolerance, improves insulin sensitivity, and lowers cardiovascular risk factors. Exercise has been shown to reduce the risk of hypoglycemia and lower serum lipid levels in patients with type 2 diabetes. In addition, weight loss is a significant factor in the therapy of patients with type 2 diabetes, and the elimination of obesity is a primary goal. In some cases, exercise and diet with weight loss is enough to control serum glucose levels without need for pharmacological intervention.

The measurement of glycated hemoglobin (the HbA1c blood test) assesses long-term glycemic control. The HbA1c represents a number that reflects the glycemic history during the previous 3 months. This measurement is the primary way to establish a prognosis for complications of DM. For example, an HbA1c of 6.6 mmol/L equals 120 mg/dl. A 1.7 mmol/L rise in HbA1c translates to a rise of 30 mg/dl serum glucose.

Pharmaceutical Treatment of Type 1 DM

Injected insulin immediately enters the bloodstream, thus patients must eat to avoid a rapid drop in blood sugar. Most patients require approximately 1.0 U/kg per day of insulin divided into multiple doses. Combinations of short (lispro), intermediate (Lente), and long-acting (Ultralente) insulin are used to prevent spiking of serum glucose levels. Continuous subcutaneous insulin infusion (CSII) has been developed to better mimic the natural secretion of insulin from the pancreas. An insulin nasal spray was approved in early 2006 to eliminate the need to constantly use a syringe for injection.

Pharmaceutical Treatment for Type 2 DM

Glucose-lowering agents are the mainstay of therapeusis for type 2 DM. These agents can increase insulin secretion, reduce glucose production, and influence insulin sensitivity. Medications that increase insulin secretion acutely by the beta cell include the first- and second-generation sulfonylureas (glipizide and glyburide) and should be taken just before a meal. Sulfonylureas act to increase insulin and will result in a drop in HbA1c. These drugs have a short onset of action and act to lower fasting blood sugar. Unfortunately, these agents can cause hypoglycemia and weight gain. Metformin acts to reduce glucose production in the liver. Its use can result in weight loss and increase use of glucose, however, metformin may result in diarrhea and nausea.

The thiazolidinediones, such as rosiglitazone, reduce insulin resistance and increase glucose use. This class of medications may improve the triglyceride profile but can result in liver damage.

Diabetic Retinopathy

Epidemiology of Diabetic Retinopathy in Type 1 DM

In young patients who develop type 1 DM, the onset of diabetic retinopathy (DR) does not occur for 3 to 5 years after the onset of the disease. Some form of diabetic retinopathy is present in nearly 100% of individuals with type 1 DM after 20 years. Approximately 50% of these individuals have proliferative diabetic retinopathy (PDR) after 15 years.

Epidemiology of DR in Type 2 DM

In type 2 DM, the onset of DR is more variable because it is more difficult to determine the actual onset of the disease. Sometimes DR is seen as the initial clinical sign of type 2 DM.

Epidemiology of Macular Edema

This form of diabetic retinopathy is more prevalent in older individuals with type 2 DM. In a young individual with type 1 DM, the presence of macular edema is almost always associated with proliferation. Approximately one fifth of type 1 DM patients develop macular edema within a decade of diagnosis, and approximately one quarter of type 2 DM patients who require insulin develop macular edema within 10 years. The prevalence of macular edema in type 2 diabetic patients who do not require insulin is approximately 14%.

Pathogenesis of Diabetic Retinopathy

Sustained high serum glucose seems to be related to the development of PDR by an as yet unknown mechanism. This state of prolonged elevated blood sugar may alter genetic expression, and the modified gene products change cellular functioning. Additionally, prolonged hyperglycemia may produce excessive oxidative stress that leads to free radical formation and subsequent tissue damage. Some metabolic state of the retina in a young person with type 1 DM may exist that creates an environment conducive towards development of retinal neovascularization.

The most recent proposed mechanism of diabetic retinopathy draws comparisons between the retinopathy and an atypical inflammatory response. Other recent proposals that attempt to explain the relationship between hyperglycemia and the development of DR include changes in certain biochemical pathways, alterations of cellular insulin receptors and glucose transporters, and polypeptide growth factors that regulate retinal vascular growth.

Risk Factors of Diabetic Retinopathy

Certainly the duration and type of diabetes influences the development of DR. Other factors include the onset of puberty (because of hormonal factors), systemic hypertension, pregnancy, genetics, and tight glucose control. Progression of the retinopathy decreases in patients with tightly controlled serum glucose. Although genetic factors may influence the progression of DR (which may explain why only 50% of type 1 patients develop proliferation after 15 years), ethnicity does not seem to be a relevant issue. Interestingly, glaucoma and myopia both seem to reduce the progression of DR.

Histopathology of Diabetic Retinopathy

All microvascular abnormalities that occur in diabetes are the result of prolonged hyperglycemia. Significant lesions occur in the pathogenesis of diabetic retinopathy. The first to occur is usually capillary membrane thickening. In addition, collagen deposits in the basement membrane of the capillary. The cause of this thickening is as yet undiscovered. As the basement membrane of the capillary thickens, a loss of intramural pericytes occurs that causes bulging from the side of the capillary wall. Ophthalmoscopically this bulging would appear as a tiny, red dot indicating the presence of a microaneurysm. This condition is the earliest observable funduscopic lesion related to diabetic retinopathy. The retinal capillary microaneurysm represents either a focal region of endothelial cell proliferation or an area on the capillary wall that has become weakened because of a loss of pericytes. Indeed, pericytes may act as a contractile unit that adds tone to the capillary wall, and loss of pericytes would theoretically create a weak point from which a microaneurysm may form.

After capillary membrane thickening, loss of pericytes, and microaneurysm formation, a breakdown in the blood-retinal barrier occurs. This breakdown is not observed clinically, but is the result of formation of fenestrations within the endothelial cell cytoplasm and opening of the tight junctions between adjacent endothelial cell processes.

Ocular Complications of Diabetes Mellitus

Individuals with DM are 25 times more likely to become legally blind than individuals without DM. In individuals between 20 and 74 years old, DR is the leading cause of blindness in the United States. Blindness in DM is usually the result of diabetic retinopathy or clinically significant macular edema (CSME).

Diabetic retinopathy is divided into nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

Nonproliferative Diabetic Retinopathy

Nonproliferative diabetic retinopathy (NPDR) is characterized by intraretinal microvascular changes in the absence of neovascularization. This stage is early and will precede the proliferative stage of DR. The clinical signs of NPDR include microaneurysms and the intraretinal microvascular abnormalities (IRMA) that occur because of retinal vascular permeability changes. Eventually, retinal nonperfusion occurs because of closure of the retinal vessels. Hemorrhages and IRMA are a direct result of nonperfusion of the retina. The characteristics of NPDR (depicted in the standard photographs of the modified Airlie House Classification of Diabetic Retinopathy of 1968 and modified by the Early Treatment of Diabetic Retinopathy Study [ETDRS] research group) include the following.

Microaneurysms

These outpouchings of the blood vessel wall occur in the retinal capillary and are visualized as tiny red dots in the posterior pole (Figure 12-3). A microaneurysm is

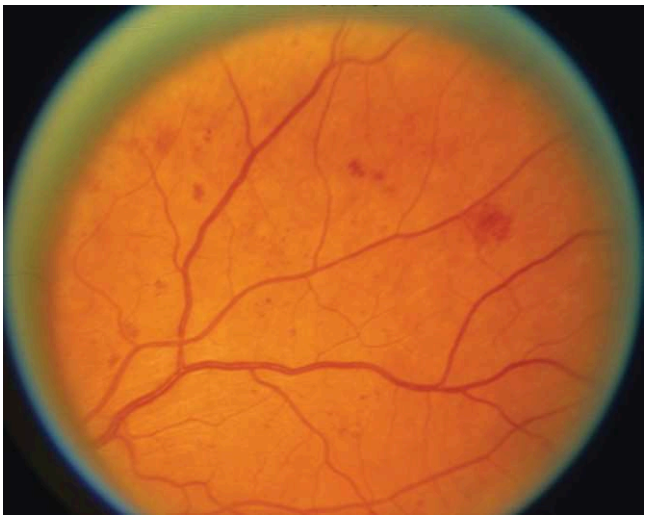

FIGURE 12-3 ■ Standard photograph 2A of the Modified Airlie House Classification of Diabetic Retinopathy demonstrating a moderate degree of hemorrhages and/or microaneurysms. (Courtesy the Diabetic Retinopathy Study Research Group.)

considered the hallmark of NPDR but is difficult to differentiate from a dot hemorrhage. Fluorescein studies are needed to distinguish the microaneurysm from the dot hemorrhage, because the aneurysmal sac hyperfluoresces and the dot hemorrhage is dark. The microaneurysms increase in number as the retinopathy develops, but no treatment is necessary at this stage.

Macular Edema

The most significant cause of vision decrease in NPDR is macular edema (ME). The ETDRS classified ME as clinically significant macular edema (CSME) if, "(a) the retina is thickened at or within 500 nm of the center of the macula; (b) hard exudates at or within 500 µm of the center of the macula, if associated with thickening of the adjacent retina; or (c) a zone or zones of retinal thickening one disk area or larger, any part of which is within one disk diameter of the center of the macula" (ETDRS report no. 1, 1985).

Retinal edema develops as the permeability of the retinal vessels increase and fluid accumulates within one disc diameter of the macula. Macular edema represents a collection of intraretinal fluid within the macular space and is often associated with retinal hard exudates visualized on slit-lamp biomicroscopy views. Macular edema is quantified by optical coherence tomography (OCT), which provides high-resolution photographs of the retina and the surrounding structures.

Hard Exudates

This extravasation of lipid deposits in the retina because of lipoprotein leakage from the blood vessels (Figure 12-4). The vessel becomes permeable because

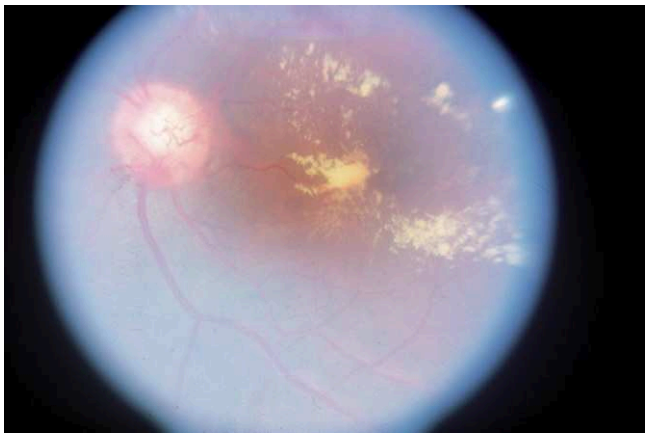

FIGURE 12-4 ■ Hard exudates in the macular area. Adjacent retinal thickening is present that is not appreciated without stereoscopic viewing.

of breakdown in the endothelial tight junctions. These exudates are yellow-white intraretinal deposits with well-circumscribed borders. They are directly related to an elevated serum lipid level.

Intraretinal Microvascular Abnormalities

These areas of tiny and tortuous blood vessels clump adjacent to an area of nonperfusion (Figure 12-5). They may represent preexisting and dilated capillaries, or they may represent early neovascularization. Intraretinal microvascular abnormalities (IRMA) occur because of retinal terminal arteriole closure with subsequent retinal hypoperfusion. As the condition progresses, IRMA becomes associated with hemorrhages and dilated retinal veins (venous beading).

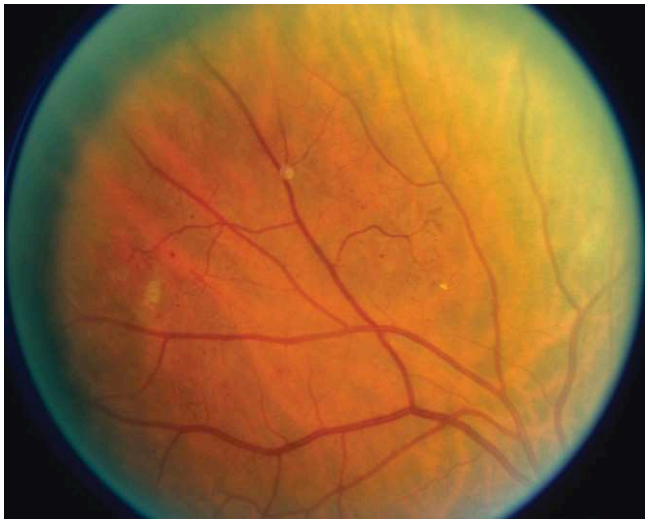

FIGURE 12-5 ■ Standard photograph SA of the Modified Airlie House Classification of Diabetic Retinopathy demonstrating intraretinal microvascular abnormalities (IRMA). (Courtesy the Diabetic Retinopathy Study Research Group.)

Cotton-Wool Spots

These soft exudates represent the presence of severe NPDR (preproliferative retinopathy). Cotton-wool spots usually disappear in 6 to 12 months.

Venous Beading

Areas of the retinal veins may dilate in a segmental fashion because of weaknesses in the walls of the vessels (Figure 12-6). If venous beading is found in two quadrants of the retina, the retinopathy is considered severe NPDR.

Classification of Nonproliferative Diabetic Retinopathy (Table 12-1)

Four levels of NPDR exist: mild, moderate, severe, and very severe. The level of severity is determined on the basis of the characteristics discussed above, including microaneurysms, hemorrhages, exudates, and IRMA. The earliest stage of NPDR is characterized by the presence of microaneurysms. Mild NPDR occurs when there are microaneurysms with retinal hemorrhages and/or hard exudates. If cotton-wool spots or mild IRMA occurs with the microaneurysms and retinal hemorrhages then moderate NPDR is present. Severe NPDR is characterized by microaneurysms plus venous beading, hemorrhages, or both. Severe NPDR is a preproliferative stage of DR and occurs because of increasing ischemia from capillary closure. The examiner should evaluate severe NPDR by dividing the retina into four quadrants and looking for hemorrhages or microaneurysms in all four quadrants. If only venous beading occurs in two quadrants of the retina, then this is also considered severe NPDR. Any single area of moderate IRMA also indicates severe NPDR. If two of these features are present, then the condition is considered very severe NPDR.

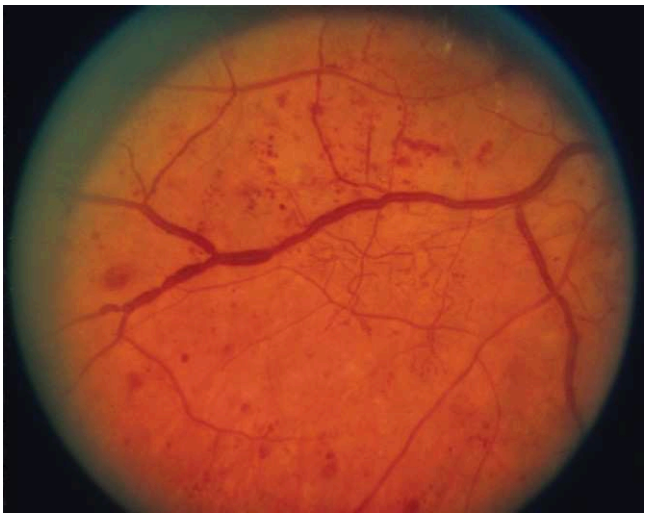

FIGURE 12-6 Standard photograph 6B of the Modified Airlie House Classification of Diabetic Retinopathy demonstrating venous beading. (Courtesy of the Diabetic Retinopathy Study Research Group.)

"4 + 2 + 1 Rule" for NPDR. In cases of NPDR, a convenient rule has been formulated to determine the presence of the severe stage. Known as the "4 + 2 + 1 rule," severe NPDR is said to exist if one of the following criteria is met: 20 or more hemorrhages exist in all four quadrants of the retina, venous beading (segmental venous dilations) is present in at least two quadrants of the retina, or moderate IRMA is present in one quadrant of the retina.

Risk of Progression to Proliferative Diabetic Retinopathy. The ETDRS has established the risk of progression of NPDR to the proliferative stage. NPDR usually begins to appear after approximately 10 years of insulin use. The mildest stage of NPDR has at least one hemorrhage, microaneurysm, or both, with no other diabetic retinopathy changes. This stage does not represent a threat to vision. Mild NPDR has a 5% risk of progression to PDR in 1 year and a 15% risk of progression to high-risk PDR in 5 years. These patients should be examined yearly.

TABLE 12-1 CLASSIFICATION OF NONPROLIFERATIVE DIABETIC RETINOPATHY

STAGE OF NPDR	CHARACTERISTICS PRESENT	ROUTINE FOLLOW-UP EXAMINATIONS (MONTHS)
No retinopathy	No lesions	12
MA only	MA only	6 to 12
Mild NPDR	MA and RH/HE	4 to 6
Moderate NPDR	MA and RH/HE and CWS/IRMA	4 to 6
Severe NPDR	MA and RH/HE (4 Q); or, VB (2 Q); or, moderate IRMA (1 Q)	3 to 4
Very severe NPDR	Two or more severe NPDR characteristics	3 to 4

NPDR, Nonproliferative diabetic retinopathy; *MA,* microaneurysm; *RH,* retinal hemorrhage; *HE,* hard exudates; *CWS,* cotton-wool spot; *IRMA,* intraretinal microvascular abnormality; *VB,* venous beading; *Q,* quadrant of the retina.

In moderate NPDR the hemorrhage/microaneurysm appearance is greater than or equal to standard photograph 2A (see Figure 12-3). In this stage intraretinal microvascular abnormalities (IRMA) are present. This stage has a 12% to 27% risk of progression to PDR in 1 year and a 33% risk of progression to high-risk PDR in 5 years. These patients should be seen every 6 months. Focal laser treatment is necessary if CSME is present.

In severe NPDR, the hemorrhages/microaneurysms are greater than in standard photograph 2A in four quadrants, or IRMA is present in one quadrant. A 50% risk of progression in 1 year to PDR and a 66% risk of progression to high-risk PDR in 5 years exists. These patients must be seen every 2 to 3 months by the eye doctor. These patients may need panretinal photocoagulation (PRP) laser therapy.

In very severe NPDR two characteristics of severe NPDR are present.

Glycemic Control in NPDR. Poorly controlled serum glucose results in increased severity of DR. The Diabetes Control and Complications Trial (DCCT) of 1993 to 1996 showed conclusively that "intensive insulin treatment is associated with a decreased risk of either the development or the progression of DR in patients with type 1 diabetes." The DCCT demonstrated that every 10% decrease in HbA1c was associated with a concurrent 40% reduction in the risk of retinopathy progression. The DCCT has been used to formulate the recommendation to keep the HbA1c below 7% in cases of DM.

Systemic Hypertension and Nonproliferative Diabetic Retinopathy. Tight control of systemic hypertension was shown to reduce retinal vascular disease and the necessity of photocoagulation.

Serum Lipids and Nonproliferative Diabetic Retinopathy. Elevated serum cholesterol was found to be associated with an increased severity of retinal exudates (Chew, 1996). Hard exudates (HE) cause several complications including reduced visual acuity and subretinal fibrosis (ETDRS). In 2004 Lyons reported that the severity of the progression of DR is directly related to elevated triglycerides and inversely related to high-density lipoproteins. No doubt seems to exist that lowering serum triglycerides reduces the risk of visual loss in cases of DM.

Pregnancy and Nonproliferative Diabetic Retinopathy. Pregnancy accelerates the progression of DR. Patients who are diabetic should have their eyes examined before conceiving and during pregnancy in every trimester. Severe NPDR in pregnant individuals should be evaluated every month (AAO, 1998).

Treatment of Nonproliferative Diabetic Retinopathy. The ETDRS of 1987 to 1991 and the Diabetic Retinopathy Study (DRS) of 1978 to 1981 studied the effectiveness of laser photocoagulation on the severity of the retinopathy and the presence or absence of CSME. In patients with severe NPDR with visual acuity of 20/100 or better who received scatter and focal photocoagulation, a 56% reduction in severe visual loss (5/200 or worse) was noted. The study showed that the risks of scatter photocoagulation did not outweigh the benefits of treatment in cases of mild-to-moderate NPDR. In cases of severe or very severe NPDR, however, scatter photocoagulation is effective in reducing severe visual loss in patients with type 2 diabetes (Ferris, 1996).

Treatment of Macular Edema. The ETDRS demonstrated that "focal/grid photocoagulation reduced the risk of moderate visual acuity loss for all eyes with diabetic macular edema and mild to moderate NPDR by about 50%." Patients with edema involving the center of the macula are at greatest risk of visual loss, but patients can notice areas of blindness caused by focal laser burns. Therefore, leakage at or near the fovea is best monitored rather than treated. Focal laser is used to treat leaking microaneurysms close to the center of the macula. Diffuse leakage is treated with a grid laser of light intensity burns. In 2004 Massin described the use of intravitreal injections of triamcinolone acetonide in the treatment of macular edema.

Definition of PDR

PDR (Table 12-2) comprises the state of newly formed blood vessels, fibrous tissue, or both that arises from the retina. The neovascular vessels, fibrotic proliferation, or both may form on the retinal surface or disc and extend into the vitreous cavity (Davis and Blodi, 2006).

Pathophysiology of Proliferative Diabetic Retinopathy

Occlusion and closure of the retinal capillary bed causes areas of inner layer retinal ischemia. A retinal angiogenesis factor is produced by ischemic retina. This chemical stimulates the growth of new blood vessels in an attempt to oxygenate hypoxic retinal

TABLE 12-2 CLASSIFICATION OF PROLIFERATIVE DIABETIC RETINOPATHY

PDR without HRC	Neovascularization/fibrous proliferation, or preretinal hemorrhage or vitreous hemorrhage
PDR with HRC	NVD > Photo 10A (see Figure 12-7); NVE with vitreous or preretinal hemorrhage
Advanced PDR	Vitreous hemorrhage; retinal detachment of the macula; phthisis bulbi

HRC, High-risk characteristics, *NVD,* neovascularization of the disc; *NVE,* neovascularization elsewhere.

cells. Angiogenesis-growth factor diffuses to the disc and causes neovascularization of the disc (NVD; Figure 12-7). As the growth factor reaches distant areas of the retina it causes preretinal neovascularization, or neovascularization elsewhere (NVE; Figure 12-8). Retinal angiogenic-growth factor may even diffuse through the vitreous to the anterior chamber to stimulate new blood vessel growth on the iris producing neovascularization of the iris (NVI; Figure 12-9).

Characteristics of New Blood Vessels

Neovascular vessels usually form within 45 degrees of the posterior pole and commonly on the disc. New blood vessels on the disc begin as thin loops, or may appear as a network of fine vessels on the surface of the disc. NVE must be differentiated from IRMA, though in either case a referral to retina specialty is mandatory. The NVE typically demonstrates a "wheel-like" network and may extend across arterial and venous branches while being accompanied by fibrous proliferations. IRMA is smaller, unorganized, and unassociated with fibrous proliferations.

Evolution of Proliferative Diabetic Retinopathy

New blood vessels begin as a fine network on the retinal surface, but with time their caliber increases to nearly the size of arterioles. The increase in size takes weeks to months. As they grow, fibrous proliferation appears as white, translucent tissue adjacent to the neovascularization. In time the new blood vessels regress and are replaced by fibrous tissue. Areas of neovascularization adhere to the posterior vitreous surface and adjacent areas of fibrous tissue contract,

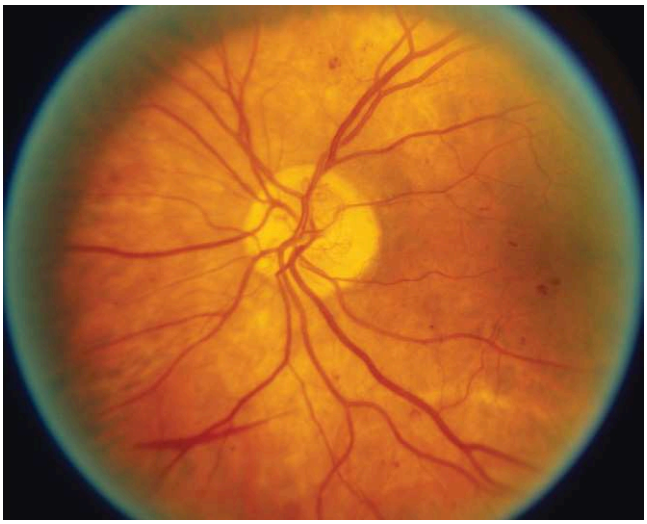

FIGURE 12-7 ■ Standard photograph 10A of the Modified Airlie House Classification of Diabetic Retinopathy demonstrating neovascularization of the optic disc covering approximately V4 to V3 of the disc area. (Courtesy the Diabetic Retinopathy Study Research Group.)

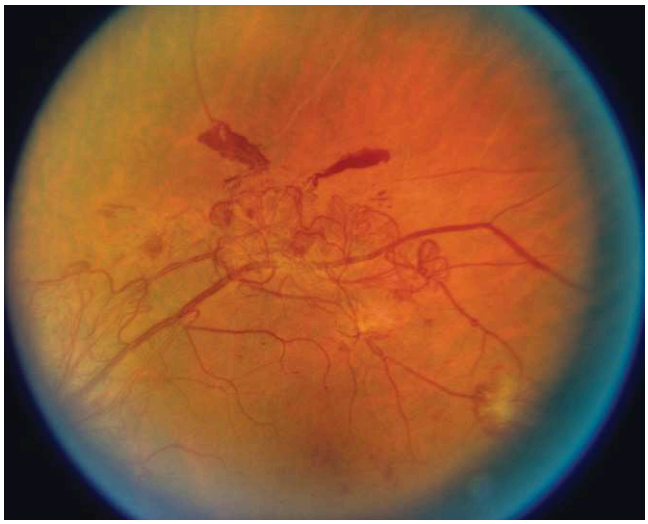

FIGURE 12-8 ■ Standard photograph 7 of the Modified Airlie House Classification of Diabetic Retinopathy demonstrating new vessels elsewhere (NVE) in the retina with fresh hemorrhage. (Courtesy the Diabetic Retinopathy Study Research Group.)

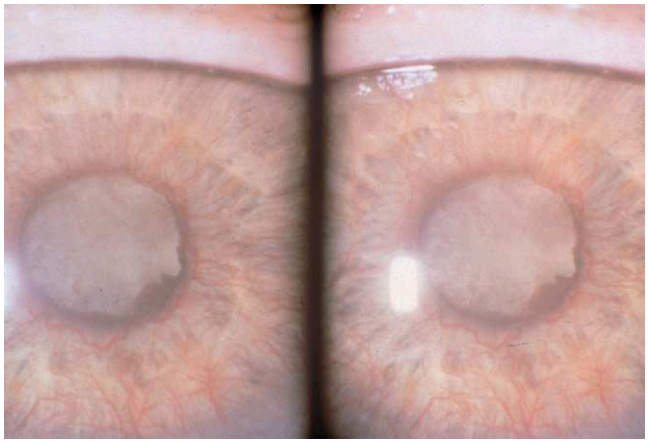

FIGURE 12-9 ■ Clinical appearance of rubeosis iridis at the pupil border.

leading to a posterior vitreous detachment. Distortion of the macula may occur when a large fibrovascular sheet contracts. This "dragging" of the macula usually occurs in a nasal direction from the disc. The same process may lead to a retinal detachment. Recurrent vitreous hemorrhage occurs because of the fragility of the newly formed blood vessels. Eventually, vitreous contraction is completed and a severe loss of vision results.

Glycemic Control and Proliferative Diabetic Retinopathy

Tight glycemic control reduces the risk of progression from NPDR to PDR in insulin-dependent diabetes by a significant amount (DCCT, 1996). In type 2 diabetes,

stringent glycemic control also reduced the risk of progression (Ohkubo, 1995).

Risk Factors for Proliferative Diabetic Retinopathy

Hyperglycemia, severe anemia, and elevated serum lipids are all significant risk factors for the development of high-risk PDR. One study showed that systemic hypertension was not a significant risk factor in the progression to high-risk PDR (ETDRS). Hypertension was shown to be a significant contributor to progression to PDR in the United Kingdom Prospective Diabetes Study, however (UKPDS, 1998).

Treatment of Proliferative Diabetic Retinopathy

Because a vasoproliferative angiogenic substance is released by ischemic retina, destruction of the involved tissues would theoretically inhibit proliferation. Patients who have PDR with NVD or vitreous or preretinal hemorrhage should have treatment immediately. Scatter, or panretinal, photocoagulation is not used in mild-to-moderate NPDR, but is reserved for severe NPDR or moderate PDR. Scatter photocoagulation should be performed in cases of extensive neovascularization in the anterior chamber. This treatment will prevent neovascular glaucoma. In patients with macular edema and high-risk NPDR, focal or grid treatment for the macular edema should precede treatment with scatter photocoagulation (ETDRS, 1987). Regression of new blood vessels occurs in days to weeks after application of scatter photocoagulation. Complications of such panretinal laser surgery include constricted visual fields, night blindness, and macular edema.

DISORDERS OF THE THYROID GLAND

Introduction to Graves' Disease

Graves' disease, or endocrine ophthalmopathy (EO), comprises the characteristics of hyperthyroidism, toxic diffuse goiter, and ophthalmopathy. The ophthalmopathy, however, may occur independently of the thyrotoxic goiter. Therefore, for endocrine ophthalmopathy to be considered a multisystem disorder of endocrine origin, it must be associated with one or more of the following clinical features: thyroid disease (that is autoimmune in nature), an ophthalmopathy that is characterized by infiltrates, and pretibial myxedema (or dermopathy).

Because clinical investigations have traditionally concentrated on the thyrotoxic goiter, little progress has been made in identifying the pathogenesis and evolution of the orbitopathy. Only recently has Graves' ophthalmopathy received the concentrated attention of researchers and clinicians alike. For this reason no consensus exists yet on the terminology to be used in describing this disorder (Box 12-1).

BOX 12-1
NAMES SYNONYMOUS WITH ENDOCRINE OPHTHALMOPATHY

Graves' eye disease
Graves' ophthalmopathy
Graves' orbitopathy
Dysthyroid eye disease
Dysthyroid orbitopathy
Exophthalmic goiter
Immune exophthalmos
Thyroid-associated ophthalmopathy
Autoimmune orbitopathy
Autoimmune ophthalmopathy

Traditionally, the term "Graves' eye disease" or "Graves' ophthalmopathy" has been widely used but remains unsatisfactory, because the orbitopathy includes Hashimoto's thyroiditis. In 1987, Volpe suggested the term "autoimmune ophthalmopathy" or "autoimmune orbitopathy," which at least identifies the physiologic underpinning of the disorder but sacrifices its relationship with thyroid disease. In 1990 Wall and How suggested that the term "thyroid-associated ophthalmopathy" be adopted to encompass all the characteristics associated with Graves' disease. Writing in 1993, Kahaly used the term "endocrine ophthalmopathy" to describe the autoimmune origin, histologic cell infiltration of the orbital tissues, and classic signs and symptoms historically ascribed to Graves' eye disease. This section refers to thyroid-associated ophthalmopathy as Graves' disease, and reserves the term endocrine ophthalmopathy for the ocular signs and symptoms associated with thyroid-eye disease.

That so much ambivalence surrounds the nomenclature of this disease suggests the larger and more complex questions facing researchers: What causes EO and how is it related to thyroid disease? In addition, clinicians are still faced with the issues of how best to diagnose and treat EO.

Optometrists can readily serve in this new focus on EO by acting in coordinated effort with endocrine researchers and clinicians to identify the at-risk group of patients before they show any manifestations of the orbitopathy. These patients can then be closely monitored by all the involved disciplines as signs and symptoms develop. Through such a rational approach, the true biochemical, immunologic, and pathologic basis for EO may at last be discovered.

This chapter presents the latest thoughts on the autoimmune nature of this disease. Also described are the diagnostic strategies available to the optometrist when evaluating a patient with, or suspected of having, EO. Finally, the medical and surgical management of EO is presented, including the use of novel drugs,

plasmapheresis, radiation therapy, orbital decompression, and corrective eye surgery.

Thyroid Disease

Graves' disease may occur independently of thyroid disease (so-called Graves' euthyroid orbitopathy), but the ophthalmopathy occurs mostly in patients with hyperthyroidism. It is clear, therefore, that these two conditions share some pathophysiologic relationship and that an understanding of thyroid disease is necessary to study the pathogenic mechanism behind EO.

Thyroid Physiology

A sensitive feedback loop exists to regulate the level of serum thyroid hormones. This modulating system is known as the hypothalamic-pituitary thyroid axis. The basal hypothalamus located in the lateral wall of the third ventricle contains nerve endings that release thyroid-releasing hormone (TRH), a tripeptide. TRH stimulates thyroid-stimulating hormone (TSH) secretion from the pituitary gland. A polypeptide, TSH is the primary agent stimulating the thyroid gland to produce two metabolically active hormones: triiodothyronine (T_3) and thyroxine (T_4). Elevated levels of T_3 (three iodide atoms) and T_4 (four iodide atoms) in turn exert a negative feedback at the level of the pituitary gland, thus reducing TSH production. Therefore, TSH is controlled by both the hypothalamic hormone TRH and the thyroid hormones T_3 and T_4.

Thyroid Function Tests

Three types of thyroid function tests exist: serum thyroid hormone tests, hypothalamic pituitary-thyroid axis tests, and direct thyroid function tests. The serum thyroid hormone tests include serum T_4, serum T_3, serum free T_4 and T_3, T_3 resin uptake, and free T_4 index.

Serum thyroid hormone tests analyze T_4 and T_3 by radioimmunoassay, which measures the total bound and unbound fractions of each. The unbound (free) levels more accurately reflect the metabolic state than do the bound levels. The normal T_4 1evel is 4 to 12 µg/dl, and the normal T_3 level is 75 to 195 µg/dl. Hyperthyroidism and hypothyroidism produce changes in serum levels of T_3 and T_4 detected in these tests. The T_4 is the standard screening procedure for diagnosing hyperthyroidism and hypothyroidism.

Another serum thyroid hormone test is serum-free T_4 and T_3, but it is difficult to perform and expensive to measure these free hormones directly. The serum thyroid hormone test most commonly used to evaluate thyroid binding is the T_3 resin uptake (T_3RU). This test does not measure circulating T_3. Instead, the patient's serum is incubated with a T_3 tracer (radioiodine-labeled T_3) and an insoluble resin to bind the remaining free T_3. The T_3 tracer has a greater affinity for the available serum binding sites, thus after incubation the fraction of the labeled T_3 absorbed on the resin is determined. What is actually measured is the amount of radioactivity bound on the resin. The T_3RU is low in hypothyroidism and high in hyperthyroidism. The normal T_3RU is 25% to 35%. The free T_4 index is a mathematical computation involving the total serum T_4 and T_3RU, and it provides a good approximation of free T_4 (normal free T_4 index = 1 to 4).

The hypothalamic-pituitary-thyroid axis tests include the serum TSH, the TRH test, and T_3 suppression test. The serum thyrotropin (TSH) level is measured by radioimmunoassay, and normal is less than 7 µU/ml. If elevated, hypothyroidism is suspected. Serum TSH is not of value in determining hyperthyroidism, because most assays are not sensitive enough to distinguish normal from low levels. A new and very sensitive double-antibody technique for measuring below normal TSH levels has been developed, however. The TSH immunoradiometric assay (TSH-IRMA) can detect low TSH levels, indicating mild hyperthyroidism.

The TRH stimulation test determines how well the pituitary can secrete TSH in response to an intravenous injection of 200 to 500 mg of TRH. A normal TSH response to TRH excludes hyperthyroidism. An abnormally low response of TSH to TRH indicates hyperthyroidism, and an exaggerated TSH response reflects hypothyroidism.

The T_3 suppression test (Cytomel) is a radioactive iodine-uptake (RAIU) test performed before and after injection of T_3, 3 times daily for 10 days. A comparison is then made of the two RAIU readings. Normally, the RAIU level is reduced to less than half during the 10-day period. If this reduction occurs, then hyperthyroidism is ruled out. The T_3 suppression test has been largely supplanted by the TRH stimulation test.

A direct test of thyroid function is the radioactive iodine uptake (RAIU) test. Radioisotope is injected and competes with stable iodine. This test is limited in its diagnostic uses and is now of primary value in the T_3 suppression test.

The eye care specialist who encounters a patient with suspected EO should have T_3 and T_4 levels run. If T_3 and T_4 are normal, then the hypothalamic pituitary-thyroid axis should be tested by a TRH stimulation test or by the more sensitive TSH-IRMA test. The TSH-IRMA may be more sensitive in diagnosing the so-called Graves' euthyroid patient. The optometrist should consult with an endocrinologist who specializes in thyroid disease for any patient suspected of having EO.

Abnormal Thyroid Function

Hyperthyroidism. The term hyperthyroidism, first used in 1907 by Mayo, describes an abnormal state produced by elevated serum thyroid hormone levels.

The most common cause of hyperthyroidism is Graves' disease, which was first recognized and described by Parry in 1825. The cause of the hyperthyroidism in Graves' disease is an autoimmune disorder that results in the formation of thyroid-stimulating immunoglobulins. These immunoglobulins are antibodies most likely directed against the thyroid cell receptor, where they mimic TSH and cause the thyroid to overproduce and release thyroid hormones. The result of Graves' disease is a diffuse goiter with infiltrative ophthalmopathy and, on occasion, an infiltrative dermopathy of flesh-colored papules on the shin known as pretibial myxedema.

The most common symptom of hyperthyroidism (Box 12-2) is excessive nervousness, accompanied by insomnia, hyperactivity, and palpitations. Patients usually note that they have lost weight despite an increase in appetite. A cessation of menstrual flow may occur. The patient may notice tremors of the digits, heat intolerance, fatigue, and weakness.

Significant clinical signs of hyperthyroidism include a prominent stare secondary to retraction of the upper lid, sinus tachycardia, goiter, thyroid bruit, hyperactive deep tendon reflexes, and vitiligo in 10% of patients. The course of the disease is varied, and the goiter may remit and spontaneously reoccur years after treatment.

The diagnosis of hyperthyroidism (Box 12-3) is made on the basis of clinical suspicion of patients who exhibit any of the above signs and symptoms, a significant history, physical examination, and laboratory testing. In most cases of hyperthyroidism the free T_4 index is elevated and establishes the diagnosis in a likely suspect. If a patient is suspected of having a hyperthyroid state but the free T_4 index is normal, then a serum T_3 measurement should be obtained. If abnormal, this condition is called T_3 thyrotoxicosis.

BOX 12-2
SYMPTOMS OF HYPERTHYROIDISM

Major symptoms
Nervousness
Hyperactivity
Insomnia
Swings of emotion

Common symptoms
Heat intolerance
Excessive perspiration
Palpitations
Increased appetite
Weight loss
Diminished menstrual flow
Muscle weakness

Occasional symptoms
Anorexia
Nausea
Vomiting
Dyspnea

BOX 12-3
PREDISPOSITIONS OF GRAVES' DISEASE

Familial predisposition
Most frequent ages: 25 to 50 years.
Ten times more common in women than men.

Three therapeutic strategies are available at present for the treatment of hyperthyroidism: drug treatment, radioiodine therapy, and surgery. Methimazole (Tapazole) and propylthiouracil (PTU) act to block the synthesis of thyroid hormones and have immunosuppressive effects. Neither drug causes permanent hypothyroidism, and treatment usually lasts a total of 12 to 18 months. In the first 3 months the serum thyroid hormone levels usually drop to a euthyroid level. These medications have some significant side effects. Antithyroid medications are advised for children and young adults or patients with small goiters and mild symptoms.

Potassium iodine has been used as a valuable adjunct to radiation therapy by blocking release of hormone from the thyroid gland. Beta-blockers have been used to reduce the hyperactive states associated with hyperthyroidism.

Adults older than 40 with hyperthyroidism should receive radioactive iodine therapy. Full amelioration of the symptoms and signs and a return to a euthyroid state occur in 75% of patients 2 to 6 months after administration of radioactive iodine. Within the first year of treatment, 15% to 20% of all patients develop hypothyroidism. Therefore, all patients undergoing radioactive iodine treatment should be made aware of the signs and symptoms of hypothyroidism.

Surgery is considered only rarely in the management of hyperthyroidism. Children and young adults should have antithyroid drug therapy before inadequate control forces a surgical decision. Patients who decline radiation therapy or who have large goiters may be candidates for surgery. Some evidence exists that thyroidectomy (near total removal of the thyroid gland) has a positive effect on EO, but not enough studies have been done to confirm this.

Hypothyroidism. If an insufficient amount of thyroid hormone results in a reduced metabolic state, then a state of hypothyroidism exists. The most common cause of hypothyroidism is Hashimoto's thyroiditis. As mentioned previously, treatment of hyperthyroidism by radioactive iodine or thyroidectomy may result in hypothyroidism.

Hypothyroidism has few early symptoms and may exist as a subclinical entity for many years before being

diagnosed. Patients have few symptoms beyond cold intolerance, peripheral paresthesias, and complaints of bloating. Hypothyroidism is diagnosed by the laboratory finding of a low free T_4 index. Unfortunately, the free T_4 index may be normal in mild hypothyroidism. The most sensitive laboratory indicator for hypothyroidism is an elevated serum TSH level (in spite of a normal T_4 index). Serum T_3 is not a sensitive indicator of hypothyroidism.

Hypothyroidism is readily treated with the use of L-thyroxine to restore normal circulating thyroid hormones. The serum TSH assay can be used to precisely adjust thyroid replacement therapy to optimize the level of circulating hormones.

Hashimoto's Thyroiditis. Thyroiditis is an inflammation of the thyroid gland, and several forms exist based on cause and pathology. Hashimoto's thyroiditis is the most common thyroid disease and the most common cause of goiter in the United States, and the most common of all autoimmune diseases.

Patients usually experience the subtle signs and symptoms of hypothyroidism with a diffuse, nonpainful, firm, and asymmetric goiter. Laboratory testing confirms the diagnosis of Hashimoto's thyroiditis. Treatment is the same as for hypothyroidism, in that administration of L-thyroxine inhibits TSH secretion and causes goiter regression. Patients sometimes receive treatment for life.

Endocrine Ophthalmopathy

Pathogenesis

For as yet unknown reasons, antibodies called thyroid-stimulating immunoglobulins are directed against the TSH receptor on the thyroid gland. HLA-DR antigens on certain cells of the thyroid may facilitate the action of these antibodies. Some evidence indicates that perhaps a bacterial or viral infection stimulates antibody production against the invading organism but that these immunoglobulins cross-react with the thyroid TSH receptor. These antibodies mimic TSH activity, causing hormonal overproduction that yields a hyperthyroid state.

The autoimmune aspects of EO are less clear. The thyroid has been established as the target site of thyroid-stimulating antibodies, and EO has been established as an autoimmune disease most frequently associated with hyperthyroidism, but the biochemical and immunologic links between the two remain largely unexplored. This fact is the result of a lack of retro-orbital tissues of patients with EO available for study. Many laboratory approaches are currently used to study the established fact that autoantibodies (T lymphocytes) are reacting against retro-orbital tissues. Such studies indicate that the eye muscles and surrounding connective tissue are the target of the autoimmune response, but the antigen for this reaction and the immunopathologic processes occurring in the orbit have not been established.

One theory that links the autoimmune nature of thyroid disease with the histologic changes in the swollen extraocular muscles suggests the presence of a cross-reactive antigen within the thyroid and the orbit. One study suggests that T cells (autoantibodies) are sensitized to orbital antigens in patients with EO. If this is the case, autoantibodies could become sensitized to orbital tissues, and these T cells could infiltrate the muscle, releasing cytokines that activate fibroblasts. It has been firmly established that these autoantibodies react with fibroblasts. The fibroblasts produce glycosaminoglycans (GAGs), which cause swelling and fibrosis of the extraocular muscles. GAGs are molecules that induce edema. This muscular edema is rich in mucopolysaccharides, and thus research efforts are currently focused on autoantibodies with cell-stimulating properties. The autoantibodies to eye muscles in patients with EO can be detected by enzyme-linked immunosorbent assay testing (ELISA), but the detection rate is less than 60%.

Diagnostic Tests and Clinical Techniques

Clinical Signs and Symptoms. In endocrine ophthalmopathy an infiltration of the extraocular muscles with chronic inflammatory cells, associated with edema and fibrosis of the connective and adipose tissue of the orbit, causes an enlargement of the retrobulbar contents leading to proptosis. The lacrimal gland may also become inflamed. Many patients with endocrine ophthalmopathy complain of a gritty foreign body sensation. Exposure keratoconjunctivitis, nocturnal lagophthalmos, lacrimal gland involvement, reduced amplitude of blinking (Pochin's sign), and a reduced blink rate (Stellwag's sign) all contribute to the symptoms of dry eye (Figure 12-10).

The exophthalmos of EO appears to be because of an increase in extraocular muscle volume displacing the

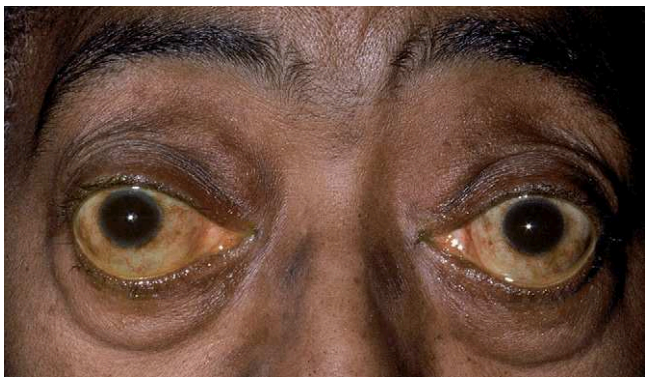

FIGURE 12-10 ■ Acute inflammatory endocrine ophthalmopathy with minimal exophthalmos and dramatic conjunctival chemosis and exposure keratopathy.

globe forward (Figure 12-11). The lid retraction (Dalrymple's sign) and lid lag (von Graefe's sign) result in a "thyroid stare" and are most likely the result of inflammatory adhesions between the levator aponeurosis and other fixed orbital tissues (Figure 12-12). The white bulbar conjunctiva above the upper limbus, usually hidden under the upper lid, is revealed. This condition is known a "baring of the sclera" (Figure 12-13).

An early sign of EO is periorbital swelling above the upper lids that is worse in the morning. This swelling may be caused by anterior displacement of orbital fat secondary to extraocular muscle enlargement or subcutaneous inflammation (Figure 12-14). Patients with more advanced EO may exhibit ocular motility restrictions (Ballet's sign; Figure 12-15) with or without diplopia. This condition is invariably the result of enlargement and fibrosis of the extraocular muscles. The most common muscle involved in EO is the inferior rectus, which causes vertical diplopia increasing on upward gaze. A weakness of convergence may also be present (Moebius' sign).

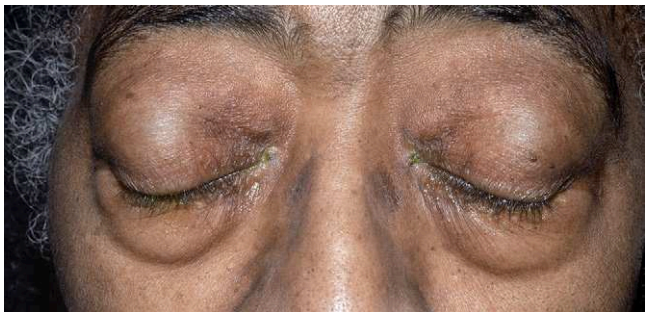

FIGURE 12-14 ■ Note periorbital swelling of the upper and lower lids, with chemosis and exposure keratopathy.

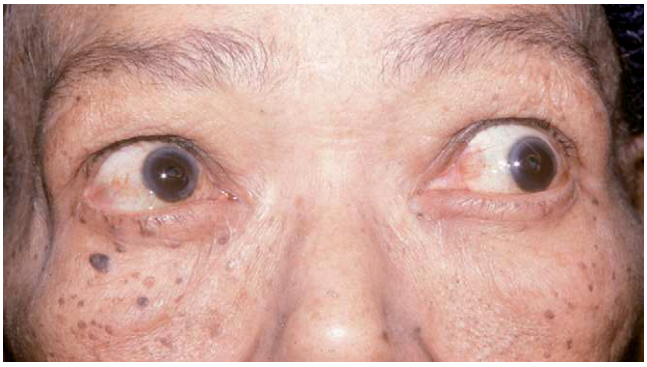

FIGURE 12-11 ■ Rapidly developing exophthalmos with marked chemosis.

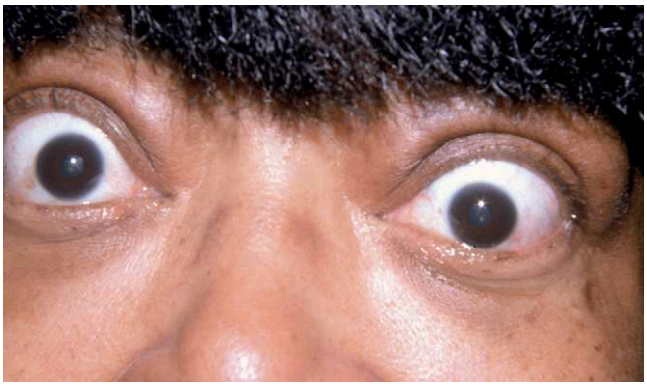

FIGURE 12-12 ■ Severe bilateral upper lid retraction in endocrine ophthalmopathy.

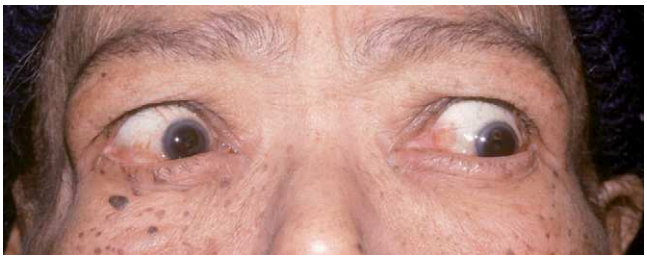

FIGURE 12-13 ■ Extreme bilateral lid retraction. Note "baring of the sclera" with no signs of conjunctival chemosis.

Visual acuity reduction in EO may occur secondary to corneal drying and induced astigmatism or from direct compression of the optic nerve by enlarged extraocular muscles. No inflammatory process appears to cause an optic neuritis, thus the optic neuropathy is the result of increased orbital volume. The greater the extraocular muscle volume, the more frequent is the optic neuropathy. Loss of color vision is also a result of this optic nerve compression. Visual field loss can occur in EO, but in no specific or predictable pattern.

Eye Signs. When diagnosing a patient with EO, the examiner should look for the following signs.

1. *Extraocular muscle signs:*
   - Ballet's sign: a palsy of one or more extraocular muscles.
   - Möbius' sign: a weakness of convergence.
   - Suker's sign: poor fixation on lateral gaze.
   - Wilder's sign: jerking of eyes on horizontal versional movements.
2. *Lid signs:*
   - Boston's sign: jerking of the upper lid as the patient looks down.
   - Dalrymple's sign: lid retraction in primary gaze (elevation of upper lid margin above its normal resting level in primary gaze).
   - Enroth's sign: edema of the lower lid.
   - Gifford's sign: difficulty in everting the upper lid.
   - Griffith's sign: lower lid lag on upward gaze.
   - Jellinek's sign: increased pigmentation of lids (Figure 12-16).
   - Joffroy's sign: absence of forehead wrinkling on upward gaze.
   - Rosenbach's sign: tremor of closed lids.

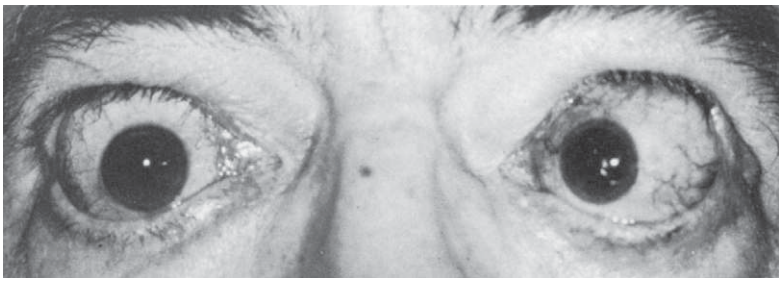

FIGURE 12-15 ■ Severe exophthalmos and eyelid retraction with fibrosis of extraocular muscles. (From Newell FW: *Ophthalmology: principles and concepts,* St Louis, 1992, Mosby-Year Book.)

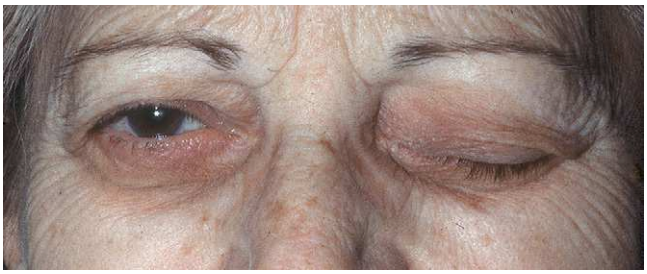

FIGURE 12-16 ■ Pigmentation of eyelids in a patient with endocrine ophthalmopathy (Jellinek's sign).

Vigouroux's sign: puffiness of lids.
von Graefe's sign: lid lag (additional lid retraction apparent in downgaze).

3. *Proptosis involvement:*
   Payne-Trousseau sign: dislocation of the globe.
   Mean's sign: increased superior sclera visible on upgaze.
4. *Pupil involvement:*
   Cowen' s sign: jerky pupillary contraction to consensual light.
5. *Blink involvement:*
   Stellwag's sign: infrequent blinking.
   Pochin's sign: reduced blink amplitude.

Differential Diagnosis. The differential diagnosis of EO includes orbital pseudotumors, orbital tumors that cause proptosis, vascular abnormalities such as hemangiomas, and cavernous sinus disease with orbital sequelae.

Diagnostic Testing (Box 12-4). It is important to quantitate the clinical signs of EO by careful and appropriate testing and documentation.

1. Proptosis measurement. Exophthalmometry, either by a Hertel or Luedde exophthalmometer, measures the amount of proptosis, with readings up to 22.4 mm being normal. This technique is best suited for measuring increases in exophthalmos over time.
2. Lid retraction measurement. To measure lid retraction in primary gaze, the examiner should hold a millimeter rule in front of the open eye and measure the amount of sclera that shows above the superior limbus. Next, the examiner should repeat the measurement as the patient looks down. Baring of the sclera and lid lag may be the first signs of EO because of inflammatory lesions of the levator aponeurosis or fibrosis of the levator muscle.
3. Periorbital swelling measurement. Periorbital swelling of the upper lid can likewise be measured with a ruler by positioning the straight edge within the upper lid fold and allowing the swollen tissue to rest on the rule. A measurement is recorded as the amount of periorbital swelling.
4. Horizontal excursion measurement. In horizontal excursions, the normal patient should be able to fully bury the lateral limbus under the lateral canthus. Limitation of horizontal excursions is demon-

BOX 12-4
DIAGNOSTIC TESTING IN ENDOCRINE OPHTHALMOPATHY

Basic ocular testing
Exophthalmometry
Measurement of lid retraction
Measurement of periorbital swelling
Measurement of horizontal exclusions

Visual analysis
Visual acuity
Slit-lamp examination
Stereoscopic analysis of optic nerve head
Color testing
Visual field testing
Pupil testing

Diagnostic imaging
Ultrasonography
Computed axial tomography
Magnetic resonance imaging

Laboratory testing
TRH
T_3
T_4
Thyroid scan
ELISA (for thyroid antibodies)

strated by sclera being exposed between the lateral canthus and lateral limbus in a fully abducted eye. This amount of exposed sclera is measured by a millimeter rule. The limitation of ductions is the best indicator of the severity of the disease.

5. Visual loss measurement. A loss of visual acuity should be assessed by visual acuity testing, slit-lamp examination of the cornea, refraction and keratometry to rule out induced astigmatism, fluorescein dye testing, and Schirmer tear analysis. Tonometry readings should be taken in primary gaze and superior gaze.

If visual loss appears to be the result of optic neuropathy, then color vision testing using the Farnsworth-Munsell l00-hue test or pseudoisochromatic plates is necessary. Automated, threshold, static visual fields are necessary to follow peripheral field losses in EO24 (Figures 12-17 and 12-18). Optic disc edema accompanied by an afferent pupillary defect may occur secondary to optic nerve compression.

Diagnostic Imaging Techniques

Ultrasonography. A-scan ultrasonography can measure the cross-sectional diameter of the extraocular muscle in question (Figure 12-19). B-scan ultrasonography produces a two-dimensional image of the muscle, and an experienced ultrasonographer is able to detect an enlarged diameter (Figure 12-20). Ultrasonography is performed without risk of radiation, in the office, and at a modest cost. It does require expertise and may miss muscle enlargement at the muscle apex.

Ossoinig has pointed out that standardized ophthalmic echography serves three functions in evaluating an EO patient: it diagnoses, confirms, or rules out EO; it follows the course and effectiveness of therapy; and it detects possible optic nerve compression. Echography confirms the presence of EO when three criteria are met: no mass lesion is detected, the orbital tissues are enlarged, and at least two extraocular muscles are thickened.

Computed Axial Tomography. High-resolution two-dimensional images of the extraocular muscles, optic nerves, lacrimal glands, and orbits can be achieved with computed axial tomography (CT) scans. Specific characteristics of EO, such as extraocular muscle enlargement, proptosis, periorbital swelling, lacrimal gland swelling, and orbital apex crowding can be demonstrated with CT (Figures 12-21 and 12-22). The CT scan yields highly detailed anatomical studies and is commonplace, but the test uses radiation and continues to be expensive.

A CT scan of the orbits in a patient with severe EO can readily detect massive enlargement of the extraocular muscles with the thin muscle in sections. In addition, compression of the optic nerve by muscles at the orbital apex can be visualized. The location of the equator of the globe can be compared with that of the lateral orbital rim to document the exophthalmos (Figure 12-23). CT sections in two planes, the axial and coronal, should be ordered when evaluating a patient with EO. The coronal sections best reveal the enlargement of the extraocular muscles and measurements are possible (Figure 12-24).

Magnetic Resonance Imaging. Magnetic resonance imaging (MRI) improves on the CT scan by allowing for

FIGURE 12-17 ■ Preoperative visual field loss because of optic nerve compression in endocrine ophthalmopathy. (From Pickardt CR, Boergen KP, eds: Graves' ophthalmopathy. Developments in diagnostic methods and therapeutical procedures. In Behrens-Baumann W, ed: *Developments in Ophthalmology,* vol 20, Magdeburg, Germany, 1989, Karger.)

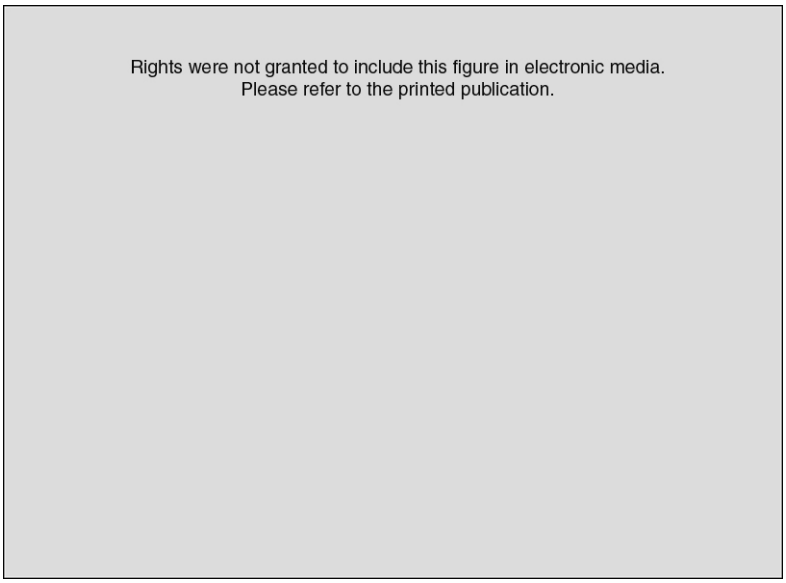

FIGURE 12-18 ■ Postoperative visual fields showing marked improvement after orbital decompression. (From Pickardt CR, Boergen KP, eds: Graves' ophthalmopathy. Developments in diagnostic methods and therapeutical procedures. In Behrens-Baumann W, ed: *Developments in Ophthalmology,* vol 20, Magdeburg, Germany, 1989, Karger.)

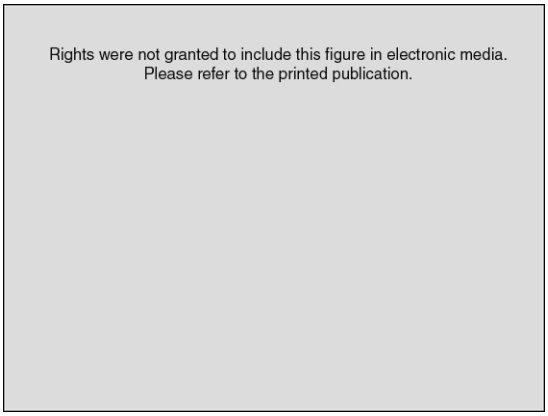

FIGURE 12-19 ■ Transocular A scan with cross-section of thickened inferior rectus muscle in endocrine ophthalmopathy. (From Pickardt CR, Boergen KP, eds: Graves' ophthalmopathy. Developments in diagnostic methods and therapeutical procedures. In Behrens-Baumann W, ed: *Developments in Ophthalmology,* vol 20, Magdeburg, Germany, 1989, Karger.)

even finer differentiation of soft tissue structure without requiring the use of ionizing radiation. MRI is not readily available, however, and is very expensive. Recently studies have shown that the T2-weighted image during MRI can accurately assess the acute inflammatory reaction within the orbital tissue. MRI sections in two planes, the axial and coronal, should be used in evaluating EO. The use of a paramagnetic contrast medium (gadolinium DTPA) has been advocated to help differentiate fibrotic extraocular muscle changes from edema.

Laboratory Testing. The ELISA may reveal antibodies to eye muscle, but the test is not specific to EO and

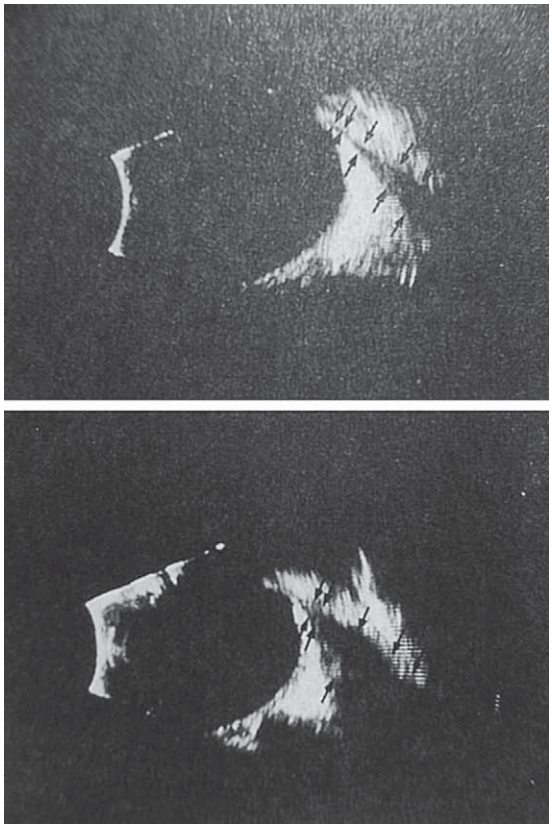

FIGURE 12-20 ■ *Top*, patient with endocrine ophthalmopathy. *Arrows* pinpoint a dark region, which is a longitudinal section of muscle surrounded by fat (*lighter zone*). Notice the thinness of muscle insertions. *Bottom,* patient with myositis. Notice thickened muscle insertions. (From Wall JR, How J, eds: *Graves' ophthalmopathy*, Boston, 1990, Blackwell Scientific.)

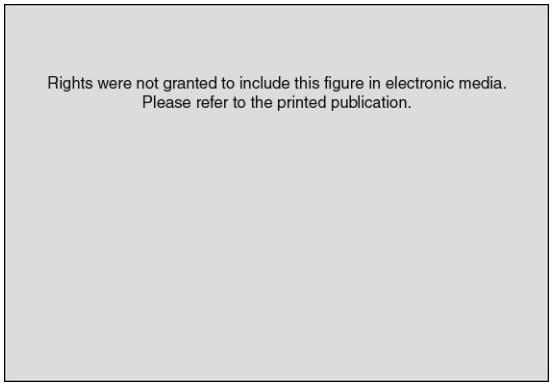

FIGURE 12-21 ■ CT scan image showing normal orbit. (From Pickardt CR, Boergen KP, eds: Graves' ophthalmopathy. Developments in diagnostic methods and therapeutical procedures. In Behrens-Baumann W, ed: *Developments in Ophthalmology,* vol 20, Magdeburg, Germany, 1989, Karger.)

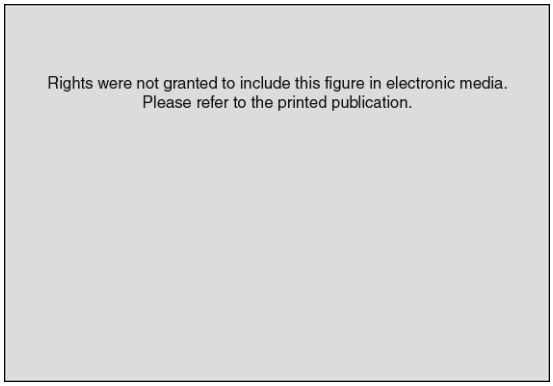

FIGURE 12-22 ■ CT scan image showing increased density of extraocular muscles in a patient with EO. (From Pickardt CR, Boergen KP, eds: Graves' ophthalmopathy. Developments in diagnostic methods and therapeutical procedures. In Behrens-Baumann W, ed: *Developments in Ophthalmology,* vol 20, Magdeburg, Germany, 1989, Karger.)

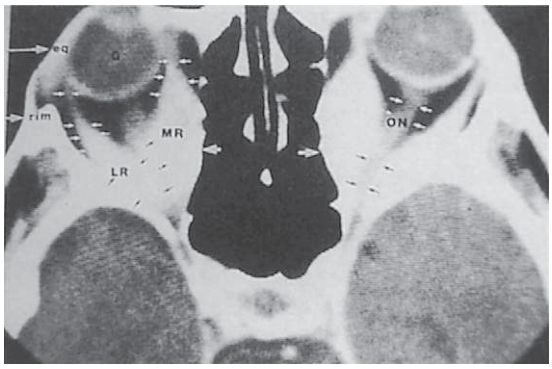

FIGURE 12-23 ■ CT scan of patient with EO. *Small arrows on the left* denote massive enlargement of medial and lateral rectus muscles. *Small arrows on the right* show compression of the optic nerve. The large arrows point to the medial walls bowing inward secondary to increased pressure. Note that the equator (*eq*) is forward of the orbital rim (*rim*). (From Wall JR, How J, eds: *Graves' ophthalmopathy*, Boston, 1990, Blackwell Scientific.)

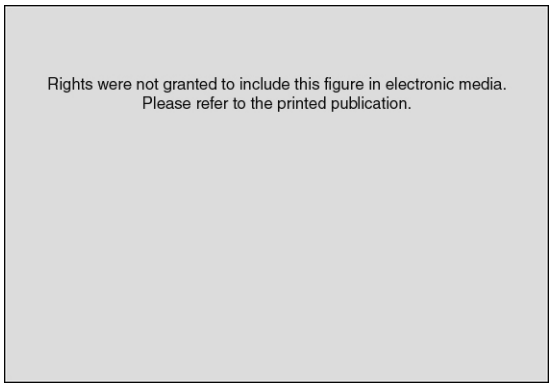

FIGURE 12-24 ■ Coronal view of enlarged right inferior rectus (*arrows*). (From Pickardt CR, Boergen KP, eds: Graves' ophthalmopathy. Developments in diagnostic methods and therapeutical procedures. In Behrens-Baumann W, ed: *Developments in Ophthalmology,* vol 20, Magdeburg, Germany, 1989, Karger.)

positive results occur in patients with other autoimmune disorders. In a patient with EO but no evidence of thyroid disease, detailed thyroid tests (TRH, T_4, T_3, and thyroid scan), thyroid antibody tests (including ELISA), and orbital scans help confirm the diagnosis. To confirm EO in a patient with hypothyroidism, ocular assessment includes exophthalmometry, measurement of lid signs, elevated intraocular pressure on superior gaze, and orbital scans.

Management (Box 12-5)

Amelioration of Risk Factor. Cigarette smoking has been shown to be a significant environmental risk factor in the development of EO. It has been postulated, but not proven, that cessation of smoking may prevent the onset of EO in genetically susceptible individuals.

Medical Management. Because of our poor understanding of the pathophysiology and evolution of EO and the lack of controlled clinical trials, managing this disorder remains difficult and controversial. The goals of medical management of EO are met if the EO is halted or reversed by antithyroid drugs and if the patient's ocular signs and symptoms are largely controlled by various local therapeutic strategies, thus avoiding significant orbital complications. Some studies point to a beneficial effect on EO with use of antithyroid medications such as methimazole. No clear evidence exists yet, however, for the mitigation of EO with antithyroid medication.

Topical Therapy. Local measures to provide symptomatic relief of the ocular sequelae of EO, such as exposure keratopathy, provide significant relief for the patient but do not modify or ameliorate the disease process. These local maneuvers include the use of artificial tear solutions by day and lubricating ointment at night. The new viscous products (such as Celluvisc) provide good relief from asthenopia for many hours. If

BOX 12-5
THERAPEUTIC MANAGEMENT OF ENDOCRINE OPHTHALMOPATHY

Local symptomatic therapy
Artificial tear solutions
Artificial tear ointment
Nocturnal lid taping
Therapeutic and collagen contact lenses
Sleep with head elevated
Corrective prisms (for diplopia)

Medical management
Antithyroid drugs
- Methimazole (Tapazole)
- Propylthiouracil (PTU)
- Potassium iodide
- Beta-blockers

Immunomodulatory drugs
- Systemic steroids
- Cyclosporine
- Methotrexate
- Cyclophosphamide
- Azathioprine

Plasmapheresis

Orbital radiation therapy

Orbital decompression

nocturnal lagophthalmos is present, taping the lids shut at night helps prevent exposure keratitis. Even dark sunglasses during the day help reduce the epiphora associated with EO. If exposure keratopathy worsens in spite of application of tear substitutes, the appropriate use of a therapeutic bandage soft contact lens may be helpful. A collagen corneal contact lens may be of value in particularly tenacious keratopathies. The patient who experiences periorbital edema that is worse in the morning should be advised to sleep with his head in a mildly elevated position.

Corrective prisms have limited use in patients complaining of diplopia secondary to EO. At best, the prisms allow for binocularity in only one particular position of gaze, because the restrictive nature of EO does not produce any consistent pattern of extraocular motility palsy. The prism correction may have to be repeatedly revised as the motility pattern changes over time. Stabilization of the diplopia may never occur, and this creates a frustrating experience for the patient.

Systemic Therapy. The goal of the medical treatment of EO is to slow or stop the inflammatory reaction in order to permit, if necessary, corrective eye surgery at an earlier stage. Medical therapy to ameliorate the actual disease process should be attempted when vision is threatened by corneal disease or optic neuropathy. Therapy consists of immunosuppressive agents given very early in the disease process when edema is causing extraocular muscle problems but no fibrosis has occurred. The oral or intravenous use of large doses of glucocorticoids has been shown to reduce soft tissue edema. Many patients have responded favorably to ACTH and cortisone, and high-dose steroids are effective in 66% of patients.

Unfortunately, large doses of steroids produce the well-known side effects in most patients. Some investigators have pointed to the potential of retrobulbar injections of steroids to reduce potential systemic side effects, but the technique has found only limited use in the routine therapy of EO. Other studies point to cytotoxic and immunosuppressive drugs such as methotrexate, cyclophosphamide, and azathioprine (which inhibits T-cell proliferation) as possibly effective in the treatment of EO, but more research is needed.

The vast majority of the literature supports the finding that two of every three patients benefit from immunosuppressive therapy. The most favorable response to immunosuppression is a reduction in soft tissue signs, with moderate improvement in motility and vision loss. The least improvement is seen in the exophthalmos, which reduces on average by only 1 mm. Immunosuppressive therapy rarely cures the eye disease, and most patients need eye surgery, albeit at an earlier time, after immunosuppression.

Plasmapheresis. Plasmapheresis, or plasma exchange therapy, is a technique to extract antibodies from the blood, which, in autoimmune disorders such as EO, should theoretically be of benefit. A typical treatment plan has the patient undergo four plasmapheresis treatments in a 1-week period, followed by steroid (prednisolone) and azathioprine given for 3 months to reduce recurrences of EO. The amount of blood that is removed is replaced by solutions of plasma proteins. Clinical trials have shown that plasmapheresis is ineffective in chronic, nonprogressive EO but is very effective in early, acute, rapidly progressive EO. One third of the patients studied had recurrence of EO 6 months after cessation of immunosuppressive therapy. All patients were stabilized by another course of plasmapheresis and a shorter course of immunosuppressive agents.

Orbital Radiation. Radiation therapy makes use of well-collimated megavoltage irradiation generated by a linear accelerator and directed at retro-orbital structures, where there is a predominance of radiation-sensitive lymphocytes in the infiltrate. Irradiation affects inflamed tissues in three ways. First, it corrects a state of acidosis by inducing ionization, thus converting the inflamed retrobulbar tissue to an alkylotic state. Second, lymphocytic activity is suppressed, thus mitigating this component of the inflammatory response. Third, fibroblasts are suppressed by radiation effects, with a consequent reduction of GAG production.

Orbital radiation therapy is well tolerated, with no long-term complications found in clinical studies (Figure 12-25). No cataract formation, radiation

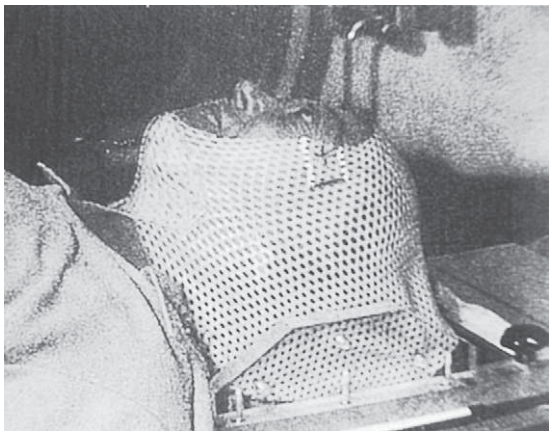

FIGURE 12-25 ■ Stable fixation of head for orbital radiation therapy (European approach). (From Wall JR, How J, eds: *Graves' ophthalmopathy*, Boston, 1990, Blackwell Scientific.)

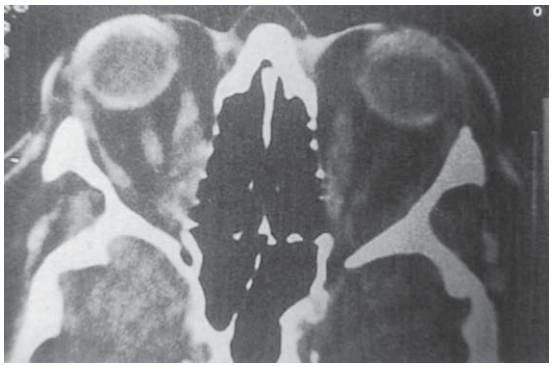

FIGURE 12-26 ■ Compression of the optic nerve by enlarged medial rectus muscle, preoperative axial CT scan. (From Wall JR, How J, eds: *Graves' ophthalmopathy*, Boston, 1990, Blackwell Scientific.)

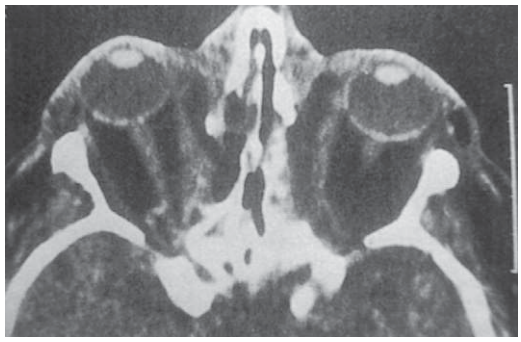

FIGURE 12-27 ■ Postoperative view of orbital decompression showing deviation of medial rectus muscles medially into ethmoidal air spaces with relief of optic nerve compression. (From Wall JR, How J, eds: *Graves' ophthalmopathy*, Boston, 1990, Blackwell Scientific.)

retinopathy, or radiation-induced tumors have been reported in treated patients. Many patients have nearly complete resolution of signs and symptoms, and only one third of radiated subjects need to proceed to surgical treatment. Studies have shown that orbital radiation therapy in most cases halts progression of the disease, and in some cases improvement of signs and symptoms occurs. Orbital radiation therapy is recommended before surgical intervention to stabilize the ocular manifestations of EO. Like plasmapheresis, it is most effective in severe, progressive EO of recent onset.

Orbital Decompression. For almost a century surgical removal of one or more of the bones that compose the bony orbit has been performed for EO. This decompression procedure allows for expansion of the enlarged orbital contents and attempts to ameliorate many of the signs of dysthyroid orbitopathy, including proptosis. An otolaryngologist usually chooses the surgical procedure, and an ophthalmologist is present to assess the operation.

The surgical approach is usually tailored to the individual patient. For example, if the patient has posterior optic nerve compression because of an enlarged medial rectus muscle but little proptosis, the medial wall is removed all the way back to the sphenoid sinus. This allows the medial rectus to expand into the ethmoidal air sinus, thus reducing pressure on the optic nerve (Figures 12-26 and 12-27). If the medial rectus and inferior rectus are involved with mild proptosis, the medial wall and medial portion of the orbital floor are removed. With significant proptosis, three- or four-wall decompression with lateral wall or orbital roof removal can help reduce the exophthalmos.

Indications for orbital decompression include marked proptosis, corneal exposure with possible keratopathy, cosmetic disfigurement, or compression of the optic nerve that threatens vision. Other indications include orbital pain and orbital congestion resistant to steroids.

Before orbital decompression is attempted, the patient should have immunosuppressive therapy in an attempt to reduce the orbital disease. If steroid toxicity develops, radiation therapy is a valuable alternative. Only after these therapies have been tried and the ocular condition has been stabilized should orbital decompression be considered (Figure 12-28).

Orbital decompression may have serious complications. It has been noticed that in some cases the lid retraction actually worsens after surgery. In some cases the cornea may be abraded or the optic nerve injured (causing visual loss) during surgery. The most common complication of orbital decompression surgery is contraction of the rectus muscles, which causes postoperative diplopia. Only surgical recession improves this condition, and this should be attempted after swelling has subsided (approximately 3 months).

The expected results of orbital decompression surgery include improvement of visual acuity, resolution

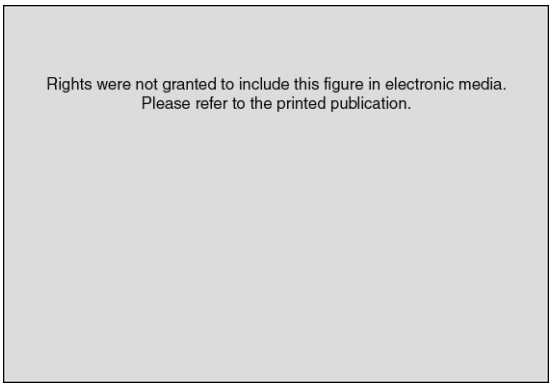

FIGURE 12-28 ■ *Top,* preoperative appearance demonstrating exophthalmos after radiation and corticosteroid treatment. *Bottom,* 2 months after orbital decompression. (From Pickardt CR, Boergen KP, eds: Graves' ophthalmopathy. Developments in diagnostic methods and therapeutical procedures. In Behrens-Baumann W, ed: *Developments in Ophthalmology,* vol 20, Magdeburg, Germany, 1989, Karger.)

of visual field defects, recession of the proptosis, and amelioration of the diplopia (Figure 12-29). Unfortunately, the correction of diplopia, one of the most troubling symptoms of EO, has a low postoperative success rate. This usually necessitates strabismic surgery to recess the involved muscles.

Corrective Eye Surgery. Patients with lid retraction are usually disturbed by the angry or surprised look that their eyes convey. In addition, they lose some of their ability to communicate nonverbally. For this reason most surgeons believe that eyelid correction is not cosmetic but functional surgery to restore facial expression and prevent corneal exposure.

Lid surgery is performed after decompression and strabismus surgery, which reduces proptosis and stabilizes the ocular condition. The surgery, which is modified for each individual case, can be performed under intravenously assisted local anesthesia (Figures 12-30 and 12-31).

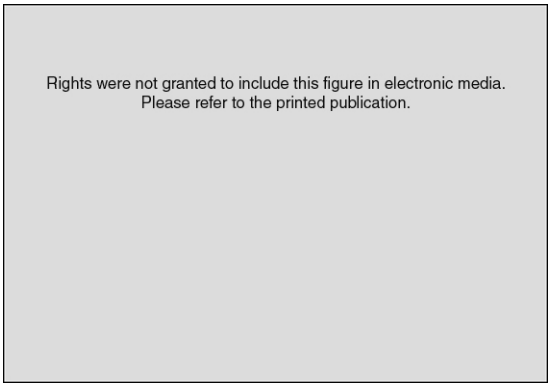

FIGURE 12-29 ■ *Top,* preoperative appearance after steroid therapy. *Bottom,* 2½ years after orbital decompression. (From Pickardt CR, Boergen KP, eds: Graves' ophthalmopathy. Developments in diagnostic methods and therapeutical procedures. In Behrens-Baumann W, ed: *Developments in Ophthalmology,* vol 20, Magdeburg, Germany, 1989, Karger.)

Summary

EO may begin with an accumulation of activated T lymphocytes (autoantibodies) that have become sensitized to cross-reactive antigens of both eye muscle and thyroid gland tissue. The antibodies release cytokines, which stimulate the synthesis of glycoaminoglycans from fibroblasts. The glycoaminoglycans produce inflammation in the extraocular muscles. The edema itself induces the expression of autoantigens on the muscle cells, thus further heightening the orbital immune reaction. The orbital tissues become infiltrated with lymphocytes, mast cells, macrophages, and fibroblasts. Muscle, connective, and adipose tissues all become pathologically altered. The extraocular muscles hypertrophy and degenerate as fat accumulates,

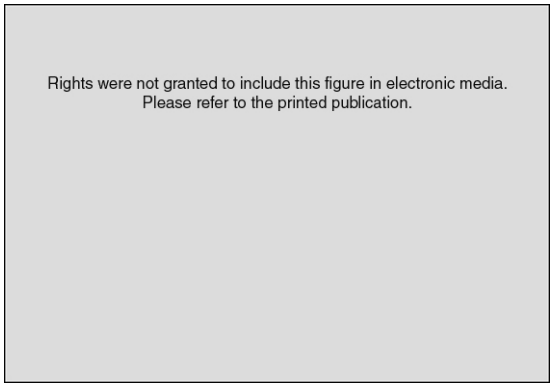

FIGURE 12-30 ■ Preoperative appearance after orbital decompression. (From Pickardt CR, Boergen KP, eds: Graves' ophthalmopathy. Developments in diagnostic methods and therapeutical procedures. In Behrens-Baumann W, ed: *Developments in Ophthalmology,* vol 20, Magdeburg, Germany, 1989, Karger.)

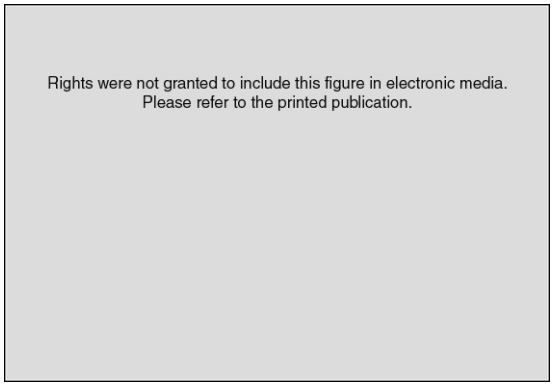

FIGURE 12-31 ■ Postoperative appearance after corrective lid surgery. (From Pickardt CR, Boergen KP, eds: Graves' ophthalmopathy. Developments in diagnostic methods and therapeutical procedures. In Behrens-Baumann W, ed: *Developments in Ophthalmology,* vol 20, Magdeburg, Germany, 1989, Karger.)

inducing the proptosis, extraocular muscle dysfunction, and periorbital edema that is seen clinically.

Some EO patients do not require therapy of any kind. If a mild orbitopathy is present, patients may be treated with local supportive efforts (artificial tears) or corticosteroids. Severe EO should be treated as soon as possible with immunosuppressants, such as cyclosporine, retro-orbital radiation, or both. Unfortunately, the combination of irradiation therapy and glucocorticoids has little effect on proptosis or diplopia.

Orbital decompression surgery is performed if medical management does not effectively halt the progress of the disease and vision continues to be threatened.

No optimal therapeutic regimen is available to reverse the orbital disorder associated with EO. This treatment will come with a greater understanding of the pathogenesis of endocrine ophthalmopathy.

DISORDERS OF THE PITUITARY GLAND

The Anterior Pituitary (AP) Gland

The AP acts to control several other endocrine glands. As such, it is often referred to as the "master gland." The AP is under control of releasing factors secreted by the hypothalamus. The AP hormones all target specific organs to release hormones the levels of which feed back and modulate the hypothalamus.

The anatomy of the pituitary gland and its surrounding structures predisposes this area to significant vascular, neuro-ophthalmic, and endocrine-based pathology. The pituitary gland sits cradled within the sella turcica. An expanding pituitary mass impacts on the nerves and blood vessels contiguous with the sella and can result in significant systemic, neurologic, and ophthalmic signs and symptoms.

Genetic Hypopituitarism

One example of a genetic-linked disease of the pituitary gland is Laurence-Moon-Bardet-Biedl syndrome. This condition causes a hypofunctional pituitary gland. Low output of pituitary hormones from the time of birth results in obesity, mental retardation and, in some cases, diabetes. The vast majority of these children develop a retinal degeneration that causes blindness by age 30.

Acquired Hypopituitarism

Hypopituitarism has several causes, including infections, degenerations, and infiltrative disease.

Infiltrative Disorders

Sarcoidosis of the pituitary gland can cause diabetes and growth retardation in children. Sarcoid is a leading cause of anterior uveitis. A child with anterior uveitis and diabetes should be evaluated for infiltrative disease of the pituitary gland.

Infective Disorders

Tuberculosis (TB) and syphilis can invade the pituitary gland and cause pituitary damage with hypofunctioning hormone levels. Both of these entities can cause recurrent anterior uveitis in association with pituitary gland involvement.

Pituitary Apoplexy

Vascular damage to the pituitary gland resulting from an acute hemorrhage may cause damage to sellar structures. Hemorrhage and subsequent infarction of the pituitary gland can result from pituitary adenoma, pregnancy, diabetes, sickle-cell anemia, and shock. Pituitary apoplexy can cause severe hypoglycemia and a critical drop in blood pressure. Patients with pituitary apoplexy develop headache, syncope, visual blurring, loss of red perception, and ophthalmoplegia. CT or MRI reveals the sellar hemorrhage. Surgical decompression is necessary in patients with visual loss and ophthalmoplegia.

Empty Sella Syndrome

MRI can reveal a partial or totally empty sella, implying the absence of the pituitary gland. Most patients are asymptomatic because of fully functioning pituitary tissue rimming the sella.

Symptoms of Hypopituitarism

Hypopituitarism causes growth disorders in children and sexual function problems in adults. Hypothyroidism results because of TSH deficiency. Blood levels of growth hormone, adrenocorticotropin hormone (ACTH), TSH and the other pituitary hormones will demonstrate the low levels of the involved hormone. Treatment of hypopituitarism uses hormone replacement therapy.

Pituitary Tumors

Adenomas are benign neoplasms that may produce pituitary hormones. They are less responsive to feedback mechanisms than the rest of the pituitary and thus cause hyperfunctional levels of the involved hormone. Pituitary adenomas are the most common cause of pituitary gland dysfunction in adults. Of the population, 25% harbor undiagnosed pituitary microadenomas. Symptoms of pituitary adenoma include changes in hair and skin texture, sexual dysfunction, gigantism (in children), and thyrotoxicosis. These tumors may also cause local pressure effects leading to cranial nerve palsy, headaches, and visual disturbance.

Because of the proximity of the optic chiasm to the sella turcica, an expanding pituitary mass can cause pressure effects on the visual pathway. As the pituitary mass expands superiorly, the ventromedial aspect of the

optic chiasm is compromised. The optic nerve fibers coursing through this region of the chiasm control the superior-lateral visual field. Therefore, as the pituitary mass expands upwards to involve the chiasm, a heteronomous quadrantanopsia involving the superior-temporal visual fields develops and expands downwards. This process eventually results in a bitemporal hemianopsia denser above. The field defect is typically bilateral but incongruous.

Cushing's disease arises from the presence of a pituitary adenoma that produces ACTH. Typically occurring in women, Cushing's disease is characterized by thin and brittle skin, obesity, high-blood pressure, easy bruising, diabetes, osteoporosis, depression, and psychosis. Surgical removal of the tumor is the treatment of choice.

Craniopharyngiomas arise from near the pituitary stalk and often involve the suprasellar cistern. These tumors are characteristically large, cystic, and partially calcified. Craniopharyngiomas can cause an increase in intracranial pressure with consequential headache, vomiting, and papilledema. A bitemporal hemianopsia denser below is typical of a craniopharyngioma impacting on the visual pathway. The tumor can cause personality disorders, weight gain, and sleep disorders. The tumor is usually surgically removed followed by postoperative radiation.

DISORDERS OF THE PARATHYROID GLAND

Four parathyroid glands are located on the posterior aspects of the thyroid gland. The parathyroid gland (PTG) regulates calcium physiology by its production of parathyroid hormone (PTH). PTH acts on bone to cause calcium reabsorption and on the kidney to stimulate calcium reabsorption.

Overproduction of PTH most often occurs from the presence of a parathyroid adenoma. Elevated PTH results in hypercalcemia, or overproduction of calcium, resulting in an elevated serum calcium level. Neuropsychological symptoms and signs of hypercalcemia include fatigue, depression, and mental confusion. Gastrointestinal and genitourinary effects of elevated calcium include nausea, anorexia, and increased urination. Cardiac effects include changes in the electrocardiogram (EKG) and arrhythmias.

Ocular signs of elevated calcium levels include the formation of a band-shaped keratopathy and calcium deposits in the conjunctiva known as lithiasis. Band-shaped keratopathy may require debridement to improve visual acuity. Conjunctival lithiasis may cause a mechanical keratitis necessitating removal of the deposit with a forceps. Young and middle-aged patients who develop band-shaped keratitis should have serum calcium and PTH levels evaluated.

The treatment of choice in cases of parathyroid adenoma is surgery, and it is usually highly successful.

DISORDERS OF THE ADRENAL CORTEX

The right adrenal gland is located adjacent to the inferior vena cava just after it emerges from the liver. The left adrenal gland is located lateral to the diaphragm and below the stomach.

The adrenal cortex produces glucocorticoids, mineralocorticoids, and adrenal androgens. These three classes of steroids modulate metabolism and immune responses in addition to blood pressure.

Steroids diffuse through the cell membrane where they bind to a receptor. This complex enters the nucleus, and the steroid binds to a specific gene. This binding pair alters genetic transcription and produces genomic effects.

A hypofunctional adrenal cortex results in reduced levels of circulating steroids. Elevated levels of steroids caused by a hyperfunctional adrenal cortex result in Cushing's syndrome.

Cushing's Syndrome

Glucocorticoids are a division of adrenal steroids the main action of which influences metabolism by enhancing the production of glucose for use as energy. The primary glucocorticoid is cortisol, or hypocortisol. Elevated levels of cortisol may be caused by prolonged use of glucocorticoids, adrenal tumors, and adrenal hyperplasia. Adrenal hyperplasia is often the result of pituitary hyperplasia. Symptoms of Cushing's syndrome include fatigue, weakness, and personality changes. The clinical signs of Cushing's syndrome include obesity, systemic hypertension, polyuria, and polydipsia. Fat deposits can occur in the eyelids and upper face causing the typical "moon" facies. Additional fat deposits may appear on the back of the neck. Posterior subcapsular cataracts may develop because of elevated glucocorticoid levels. The treatment of Cushing's syndrome depends on the etiology, although in most cases of adrenal tumors surgical excision is the treatment of choice.

Addison's Disease

Characterized by primary adrenocortical deficiency, this rare disorder is caused by adrenal gland destruction, usually from TB and histoplasmic granulomatous infiltration. Patients become weak and typically experience nausea and vomiting. Skin changes including pigmentation are accompanied by weight loss. The hyperpigmentation of the skin causes a classic bronzing of the elbows, hands, and nipples. Treatment involves the specific hormone replacement of glucocorticoids and mineralocorticoids.

PHEOCHROMOCYTOMA

This type of tumor is found most often in the adrenal medulla, although some extraadrenal pheochromocytomas develop around the sympathetic ganglia. A tumor that produces, stores, and secretes catecholamines, the pheochromocytoma is a significant cause of secondary systemic hypertension. It is easy to treat, but left untreated it may cause death. The tumors are typically small and benign.

The catecholamines released by a pheochromocytoma include epinephrine, norepinephrine, and dopamine. Release of these substances causes hypertension, anxiety attack, headache, profuse sweating, palpitations, and arrhythmias.

The treatment of choice is surgical excision of the tumor.

MENOPAUSE AND DRY EYE

During female menopause, a progressive loss of ovarian function culminates in the final episode of menstrual bleeding. After menopause, significant hormonal changes occur resulting in physiological complications. Post menopause, the female hormones estrogen and androgen are reduced, resulting in hot flashes, skin atrophy, decreased breast size, and osteoporosis. Estrogen deficiency causes the vaginal mucosa to atrophy, and presumably a related phenomenon impacts the goblet cells of the conjunctiva. This process results in dry eye and keratitis sicca.

Postmenopausal women are at risk for keratitis sicca. The dry-eye patient complains of a gritty, foreign-body sensation, usually in both eyes. Contact lens wear becomes problematic as the condition progresses. As the mucus component of the tears is reduced, the tear layer begins to break up. Evaporation of the tears results in an absence of corneal villa, with a subsequent increase in tear breakup time. The corneal epithelium becomes disrupted as degenerated epithelial cells are sloughed off. Profuse staining may be seen, a clinical indication of dry eye. As the condition worsens, the cornea may become compromised and pacified with reduction of visual acuity.

The treatment of keratitis sicca typically begins with artificial tears. Used several times daily, these supplements may increase tear viscosity, reduce evaporation and tear breakup time, and allow for corneal healing. Artificial tear ointments may be used at night. In profound cases of keratitis sicca, taping of the lids at night to minimize nocturnal lagophthalmos may also speed corneal healing. Anecdotal reports seem to indicate that oral supplementation with fish oils and flax seed oil may also help ameliorate keratitis sicca and reduce dry eye complaints, but more research is needed to verify these effects.

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CHAPTER 13

Disorders of the Immune System

CHAPTER OUTLINE

THE INNATE IMMUNE SYSTEM

Over the span of millions of years, the human body has developed two primary mechanisms to protect the host from invading pathogens. The most ancient of these defenses is the innate immune system that, inherited from the invertebrates, consists of host cells that recognize pathogens and destroy harmful microbes. This innate system must be able to perform this function while not destroying either beneficial microbes or common and benign organisms. In addition, the innate system must recognize host tissue and not initiate an immune response against self molecules.

The innate immune system acts by use of cellular components that, on contact with a pathogen, destroys the microbe. The cells involved in innate immunity include, among others, natural killer (NK) cells, macrophages, neutrophils, basophils, eosinophils, and mast cells, among others. The soluble products of the innate immune system include elements of the complement system, which is a cascade of plasma enzymes formulated to lyse pathogens or target them to be phagocytized by the neutrophil.

Derangement of the innate immune system causes immune disorders. For example, failure to recognize an invading pathogen, as in HIV/AIDS (see Chapter 14), may allow the microbe to infect the host and cause disease. Alternately, an inappropriate response to an invading substance, as occurs in some cases of uveitis, may cause significantly more damage to the host tissues than is necessary. In addition, in the absence of a true infection, the innate immune system may cause debilitating inflammation by failure to recognize host tissue.

THE ADAPTIVE IMMUNE SYSTEM

The innate immune system stimulates a cascade of reactions that stimulates a second component of immunity: the adaptive immune system. The adaptive immune system is a recently evolved defense mechanism and is found only in vertebrates. Adaptive immunity is

mediated by plasma cell proteins known as antibodies. The five types of these immunoglobulins (Igs) are designated IgA, IgD, IgE, IgG, and IgM.

Antibodies are cells with receptors for foreign or self molecules. The receptors of the antibody bind with these foreign molecules, or antigens. Once bound by the antibody, the antigen is processed and eliminated from the host by lysis or by a protective immune inflammation. The advantages of the adaptive immune system are its ability to recognize specific antigens and its immune memory.

The adaptive immune system generates two antigen receptors: the T and B lymphocytes. These cells possess unique antigen receptors that recognize the diverse molecules on the surface of pathogens and environmental substances. In addition, the adaptive immune system recognizes self antigen to bring specificity to the immune response. Formed in the thymus, T cells are lymphocytes that contain surface receptors for antigens. B cells are lymphocytes that form in the bone marrow and contain surface receptors for antigens that, once bound, stimulate the production of immunoglobulin and specific antibody to that antigen.

The cellular interactions in the regulation of normal immune responses of the adaptive system begin with stem cells that are stimulated to differentiate into either T cells, B cells, or dendritic cells. The dendritic cells process foreign antigens which present fragments of this foreign antigen to the T cell and B cell. The T cell is activated to become a killer T cell. Antigen bound to the B cell receptor complex allows for B cell maturation into an Ig-secreting plasma cell, and also provides future antibody protection against the same antigen.

THE IMMUNE RESPONSE

A coordinated defensive system is stimulated by the presence of a foreign microbe or substance within the organism. An orderly progression of events occurs that leads to the ultimate inflammatory response that protects the host from foreign antigen. An antigenic challenge first stimulates a migration of leukocytes to the local site of involvement. Next, nonspecific recognition of the antigen occurs by cells of the innate immune system such as the macrophage and basophil. This event is followed by the adaptive immune system T cell and B cell recognition of a specific foreign antigen. The resulting inflammation is then amplified by both a specific killer cell response and a chemical response that includes components of the complement system and release of cytokines, kinins, and mast-cell products. Finally, the antigen fragments and the antigenic particles are removed by phagocytosis by the macrophage and neutrophil.

THE BASIS OF IMMUNE DISORDERS

A derangement of any of the host immune defenses can cause host tissue damage and result in clinical disease. The histopathological basis of the vast majority of immune disorders follows one of three scenarios. In some cases (such as allergy) the resulting immune response is so exaggerated that the damage produced by the inflammation is far greater than would have been produced by the microbe or substance. In other instances, a condition of reduced immune response or immune deficiency may allow an invading organism to overwhelm the host. Finally, the immune system may fail to recognize host tissue with a resultant inflammatory response against self molecules that produces autoimmune disease.

ALLERGY

Histochemical Basis of the Allergic Response

An allergic response is an exaggerated immune response that results in host tissue damage. As such, these responses represent hypersensitivity reactions associated with the binding of a specific antibody, IgE, to the mast cells and basophils. Once bound, these cells become sensitized for antigen-specific activation. Presentation of the stimulating antigen to receptor-bound IgE results in a cascade of biochemical reactions within the mast cell, resulting in the release of membrane-free granules that contain the mediators of the allergic response.

The Pathophysiology of Allergy

Mast cells are distributed primarily throughout the skin and mucosal membranes. Additionally, these cells are found deeper in tissues that surround venules. Characteristic of mast cells is their quick response time that aids in their ability to prevent entry of foreign substances. When challenged with a specific stimulus, the mast cell releases histamine, causing an increase in venule permeability. Plasma proteins, elements of the complement system, and immunoglobulins migrate from the venule to the involved site, and leukocytes help to defend the host tissue.

Allergic inflammation appears to have an immediate and a late phase, and evidence of this is seen in the human response to an allergic challenge. Early in the presentation of an allergic antigen, the immediate mast cell IgE-mediated response to the local challenge includes an itchy nose with watery discharge, mucous secretion from the lungs, and wheal formations in the skin. Symptoms of the atopic allergy produced include hay fever, asthma, and eczema. Biopsy of the involved tissues after 8 hours of involvement demonstrates cells

of the innate immune system and T cells of the adaptive immune system. Thus, the allergic response represents an early mast cell response followed by a late response composed of the other cells of the innate and adaptive immune systems.

Sensitization

A requirement for an allergic response is the previous exposure of the individual to a specific antigen. Known as sensitization, the process begins with cells on the individual that sample the outside environment. These macrophage-like cells are found primarily in the eyes, nose, lungs, and intestines. The cells collect the antigen and present the foreign molecules to T cells. The antigen thus presented then becomes an allergen, and the T cell is induced to produce an allergic response. One example of this mechanism is contact dermatitis. Another response activates B cells that then transform into plasma cells. These plasma cells release IgE into the serum, and this antibody binds with mast cells and basophils. These IgE receptor-bearing cells can then become activated by exposure to the allergen.

IMMUNOPATHOLOGY

Immunopathology is the study of the protective immune mechanisms against disease known as hypersensitivity reactions. The traditional classification scheme of hypersensitivity reactions proposed by Gell and Coombs is the most widely known and divides immune mechanisms into four types.

Type I reactions are known as immediate hypersensitivity reactions and involve immunoglobulin E (IgE), histamine, and other mediators from mast cells and basophils. The binding of IgE to the mast cell and basophil activates these cells, and the release of mediators is triggered by the interaction of the antigen, or allergen, with receptor-bound IgE. These chemical mediators of allergy cause the pathophysiological responses that include increased vascular permeability, contraction of smooth muscle, and activation of other inflammatory cells and mediators. In the eye, type I ocular hypersensitivity reactions are responsible for acute allergic conjunctivitis, hay fever conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis (GPC). Atopy is the genetic predisposition to make IgE antibodies in response to allergen exposure. An atopic patient is one who is prone to IgE-mediated allergies.

Type II reactions are known as cytotoxic hypersensitivity reactions and involve immunoglobulin G and other complement-fixing (C1-binding) antibodies against normal or foreign cells or tissues. These immunoglobulins bind complement and initiate a cascade of events similar to immune-complex deposition which result in cell lysis and tissue injury. Type II-mediated reactions occur in pemphigus vulgaris, cicatricial pemphigoid, and Mooren's ulcer.

Type III reactions are known as immune-complex reactions and occur after antibody-antigen complexes are deposited in the tissue. The formation of an antibody-antigen complex is an effective mechanism to clear the antigen but may result in host tissue damage. Host tissue damage occurs when antibody-antigen complexes circulate freely and are not cleared by the reticuloendothelial system. Instead, these immune complexes are deposited in blood vessel walls and the renal glomeruli. Thus, these reactions are involved with collagen-vascular diseases, such as systemic lupus erythematosus and rheumatoid arthritis and erythema multiforme.

Type IV hypersensitivity reactions are known as delayed hypersensitivity reactions or cell-mediated immunity and are mediated by mononuclear leukocytes rather than by antibodies. T cells and macrophages mediate the reaction, and a delayed hypersensitivity reaction is noted that lasts from hours to days from the time of antigenic challenge to an observable clinical response. This reaction occurs in contact conjunctivitis, phlyctenular keratoconjunctivitis, and corneal graft rejection. Systemically, type IV reactions result in granulomatous inflammation and are associated with histoplasmosis tuberculosis, chlamydial infection, and temporal arteritis.

More recently, Sell and others proposed a classification system that divides the immunopathologic responses into seven categories, including inactivation/activation antibody complexes, cytotoxic antibody reactions, immune-complex reactions, allergic reactions, T-cell cytotoxic reactions, delayed hypersensitivity reactions, and granulomatous reactions. This system accounts for the chronic allergic inflammation often seen associated with immediate hypersensitivity and also emphasizes the importance of the T cell in cytotoxic reactions.

Type I Hypersensitivity Reactions

Immediate hypersensitivity reactions are mediated by IgE, but T and B cells play important roles in the development of these antibodies. In genetically prone individuals, an allergic reaction first requires sensitization to a specific inhaled or ingested allergen. This allergen is processed by dendritic cells that migrate to the lymph nodes, where the antigen "arms" cells (TG0 cells) that bear receptors for the specific antigen. B cells also bind to the allergen through allergen-specific receptors. Next, they process the allergen and present it to specific cells, and through a cascade of events immunoglobulin M production is switched to antigen-specific IgE production. IgE antibodies then

bind to receptors on surface of basophils. Any reexposure to the antigen results in the antigen binding to and cross-linking with antibodies on mast cells and basophils. This binding stimulates the release of chemical mediators including histamine, prostaglandins, and bradykinin, among others.

Histamine is a mediator that is released on degranulation of the mast cell and basophil and acts on receptors to cause pruritus, increased vasopermeability and vasodilation, increased airway mucus production, cutaneous vasodilation, and gastric acid secretion.

Prostaglandins are produced mainly by the mast cell. Prostaglandins act as bronchoconstrictors, peripheral and coronary artery vasoconstrictors, platelet aggregation inhibitors, and enhancers of histamine release.

Bradykinin is released from the mast cell to increase vasopermeability, vasodilation, and smooth muscle contraction, and is known to cause the pain associated with type I hypersensitivity reactions.

Type I Hypersensitivity: Clinicopathologic Correlates

Urticaria

This well-circumscribed wheal involves only the superficial portion of the skin. The wheal consists of a raised, erythematous area and is commonly referred to as a "hive." Typically reddened and pruritic with a blanched center, urticaria may consist of several disseminated wheals and may be body wide. It may be caused by any number of instigating substances including pollen, food, mold, temperature changes, sun-exposure, and drugs. Often the stimulating antigen is never identified. Once exposure occurs, the urticarial involvement has a rapid onset and is usually associated with intense itching, or pruritus. Angioedema is a swelling of the affected areas that occurs if the urticaria involves the deeper layers of the dermis and subcutaneous tissues. Treatment involves the immediate removal of the offending agent and the use of antihistamine oral agents. Glucocorticoids are effective in the short-term relief of urticaria.

Anaphylaxis

Anaphylaxis is a life-threatening response in a sensitized individual that appears within minutes after exposure to the offending agent. Death may occur quickly because of respiratory distress, vascular collapse, and shock. An individual is predisposed to anaphylaxis by preexposure to such antigens as hormones (insulin), enzymes (streptokinase), pollen, dust mites, cat dander, food, latex rubber products, bee venom, and drugs. Once exposed, the individual's response is almost immediate and includes a "tightening" or constriction of the airway because of a mechanical obstruction of the epiglottis and larynx, audible wheezing, urticaria, and vascular collapse. Immediate recognition of this condition is necessary for appropriate treatment, because death can occur in minutes. To control the urticaria, 0.2 to 0.5 ml of 1:1000 epinephrine is injected subcutaneously (and repeated in 20 minutes in severe cases). If the antigen is injected, absorption can be minimized by the application of a tourniquet proximal to the location of the site of administration. Oxygen is delivered through nasal catheter and injected or oral antihistamines are administered.

Allergic Rhinitis

The typical symptoms of allergic rhinitis include sneezing, obstructed nasal passages, nasal itching, and erythema of the skin around the nose and eyes. Symptoms typically occur after exposure to a known airborne allergen, which is typically seasonal and well-known in the patient's history. Most often, the pollen of trees, grass, and weeds that are distributed through wind will result in seasonal allergic rhinitis. Once inhaled, the pollen granule lodges in the folds of the nasal mucosal membrane, and mucosal proteins digest its outer coat. This process releases antigens that stimulate an eosinophilic response with basophils and neutrophils. IgE fixes to the surface of mast cells of the mucosal membranes, and basophils release histamine. The result is tissue edema, eosinophilic migration, and subsequent swelling of the turbinates of the nose. Diagnosis is made on the basis of the clinical observation of nasal and ocular pruritus, runny nose, sinus congestion, and conjunctivitis that occurs repeatedly during the same time of year. Spring and fall are the most common seasons for allergic rhinitis. Oral antihistamines and decongestants may offer some amelioration of the acute symptoms of allergic rhinitis. Cromolyn sodium nasal spray is effective on a continual basis for the relief of rhinitis without substantial side effects. Steroid nasal sprays are effective in the acute relief of nasal congestion and pruritus, but are known to elevate intraocular pressure in patients with steroid-linked glaucoma. Hyposensitization allows for immunotherapy of known offending agents and involves repeated exposure through injection of the antigen throughout the year.

Allergic Conjunctivitis

Classic symptomology of allergic conjunctivitis includes intense itching, burning, and watery eyes. These symptoms usually occur suddenly on exposure to a known allergen, or seasonally, as reflected in the patient's history. The clinical signs of allergic conjunctivitis include bilateral injection of the bulbar conjunctiva, a ropy or stringy mucopurulent discharge (Figures 13-1 and 13-2), and possibly but not frequently, corneal epithelial stippling. When the patient rubs his or her eyes, an influx of eosinophils into the surrounding tissues

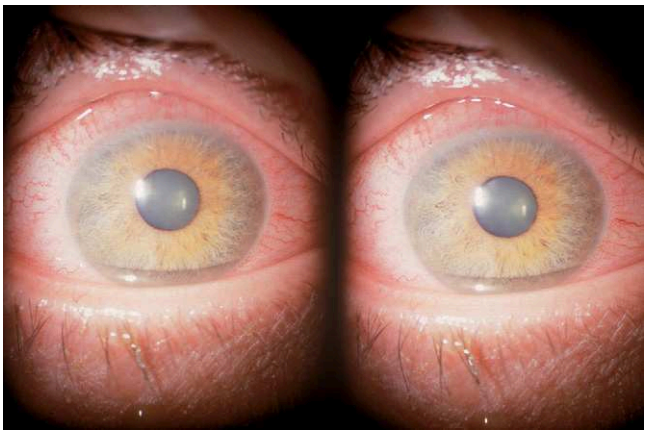


FIGURE 13-1 ■ Allergic conjunctivitis. Ocular hay fever: a type I hypersensitivity disease.

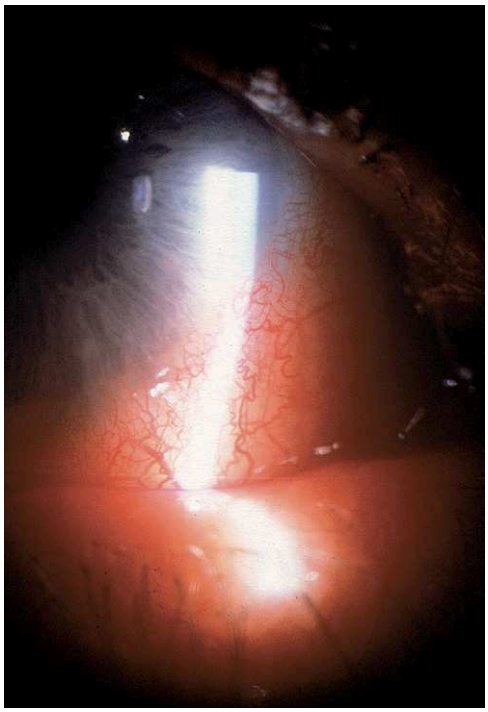


FIGURE 13-2 ■ Vernal keratoconjunctivitis. Note ptosis, conjunctival injection, and a ropy, thick discharge.

causes swelling and lid edema. The constant rubbing of the eyes increases the likelihood of mast cell and basophil degranulation, with subsequent release of histamine and bradykinin. This release provokes an ever-increasing amount of ocular pruritus. In addition, the chronic rubbing of the eyes produces dark circles on the lower lid caused by repeated breaking of subcutaneous blood vessels. Related clinical findings include nasal congestion, sneezing, and postnasal drip.

Treatment of allergic conjunctivitis includes the use of decongestants, antihistamines, mast cell stabilizers, nonsteroidal antiinflammatory drugs (NSAIDs), and topical steroids. Topical decongestants, such as phenylephrine and naphazoline, constrict conjunctival blood vessels, and thus decrease conjunctival edema and hyperemia. Topical antihistamines, such as olopatadine (Patanol) and ketotifen fumarate (Zaditor), inhibit the release of histamine and other mediators from the mast cell and thus inhibit itching, redness, chemosis, and lid swelling. Topical mast cell stabilizers, such as cromolyn sodium and lodoxamide, inhibit mast cell degranulation and reduce the release of the mediators of allergy. NSAIDs, such as ketorolac (Acular) and diclofenac (Voltaren), inhibit prostaglandin synthesis and thus reduce itching and improve erythema, edema, and mucous discharge. Topical steroids, such as FML and Pred Mild, inhibit the lymphocyte activity, decrease the number of T and B cells, and improve the signs and symptoms of inflammation. Oral versions of these medications may be effective in the amelioration of allergic conjunctivitis, but have potential and unwanted side effects that are often avoided with the use of topical agents.

Atopic Dermatitis

This condition is characterized by an eczematous cutaneous eruption with associated pruritus (Figure 13-3). Atopic dermatitis usually occurs in children and causes chronic skin scratching leading to severely excoriated or cracked skin lesions. It occurs in genetically predisposed individuals and is caused by an IgE response to antigens. Allergic immunogens include the byproducts of environmental antigens, including dust mites, cockroaches, pollen, food, and animal dander. Severe corneal involvement in chronic atopic dermatitis can cause keratoconjunctivitis with corneal neovascularization and pannus (Figure 13-4). Marginal ulceration of the cornea can occur in chronic atopic keratoconjunctivitis, and marginal blepharitis is a common complication of atopic dermatitis that can produce marginal immune corneal ulcers (Figures 13-5 and 13-6). Treatment includes avoidance of the offending allergen if possible, proper hydration of the skin, and topical glucocorticoids in the acute stage. Chronic atopic dermatitis may produce blepharochalasis (Figure 13-7).

Type II Hypersensitivity: Clinicopathologic Correlates

Pemphigus Vulgaris

Pemphigus vulgaris is a blistering skin disease seen primarily in the elderly population. A loss of adhesion between skin cells occurs that results in blisters atop normal or erythematous skin. The most common affected areas include the oral mucosa, scalp, face, and trunk (Figures 13-8 and 13-9). Ocular pemphigus vulgaris causes inflammation of the conjunctiva and the lesions may open causing pain. Healing of the

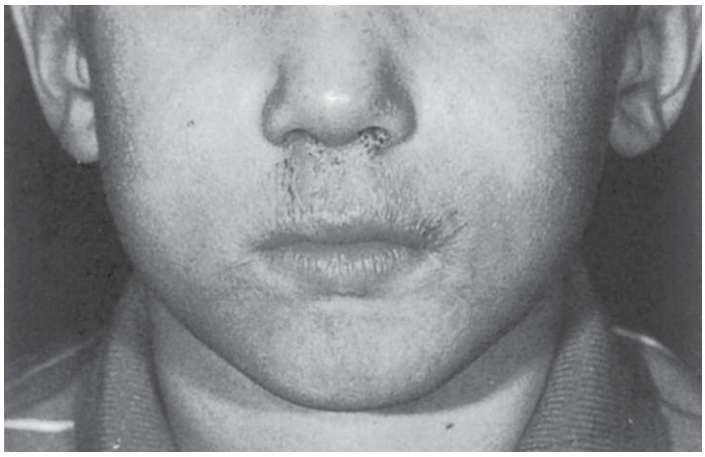


FIGURE 13-3 ■ Atopic dermatitis. Perioral involvement is common. The lips are dry and scaly. (From Habif TB: *Clinical dermatology,* St Louis, 1990, Mosby-Year Book.)

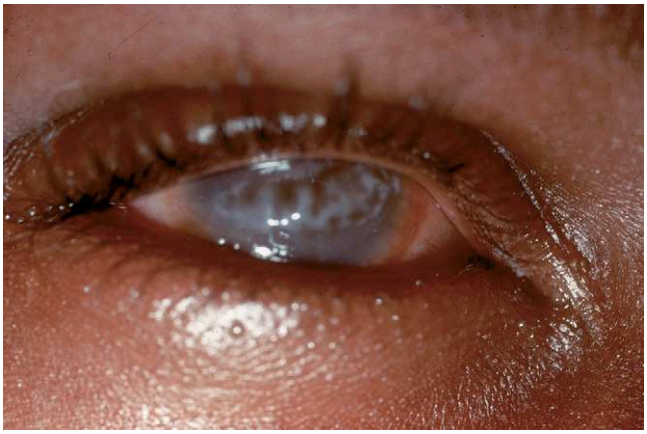


FIGURE 13-4 ■ Severe corneal involvement in atopic keratoconjunctivitis with corneal neovascularization and pannus.

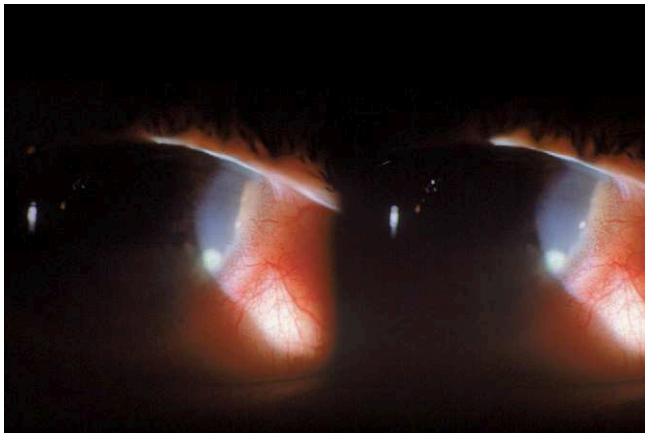


FIGURE 13-6 ■ Marginal immune corneal ulcers.

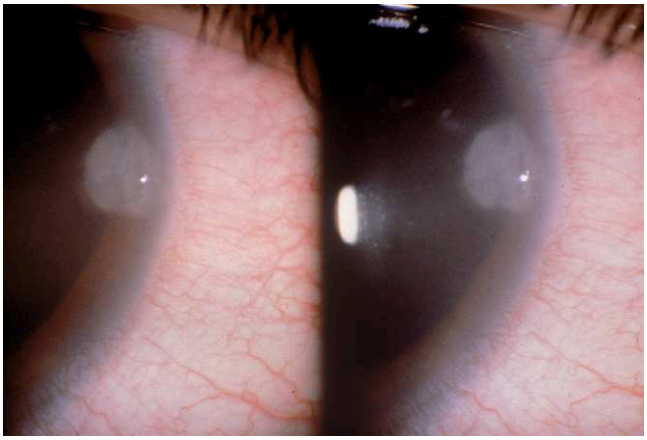


FIGURE 13-5 ■ Marginal ulcer caused by atopic keratoconjunctivitis.

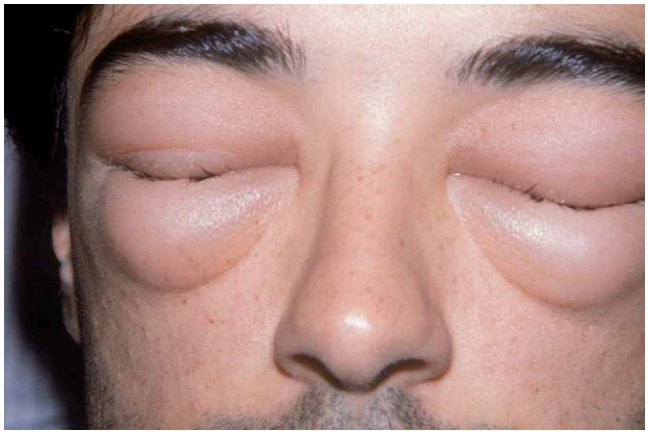


FIGURE 13-7 ■ Acute atopic dermatitis of the upper and lower lids. Note the swollen, edematous, and taut skin of both lids.

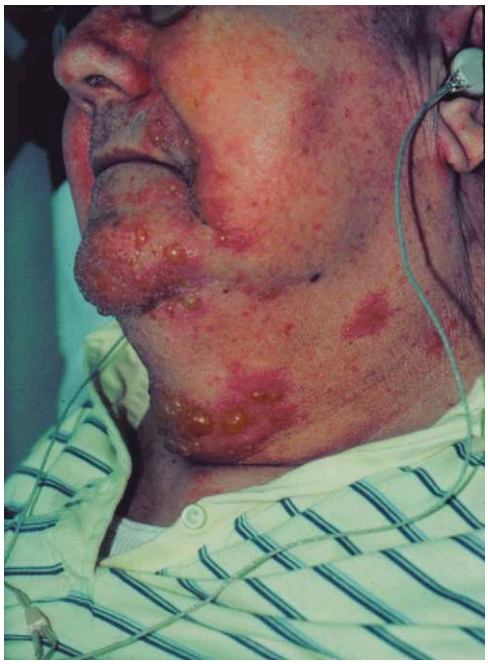


FIGURE 13-8 ■ Bullous vulgaris. (From Marx J, Hockberger R, Walls R: *Rosen's emergency medicine: concepts and clinical practice,* ed 6, St Louis, 2006, Mosby.)

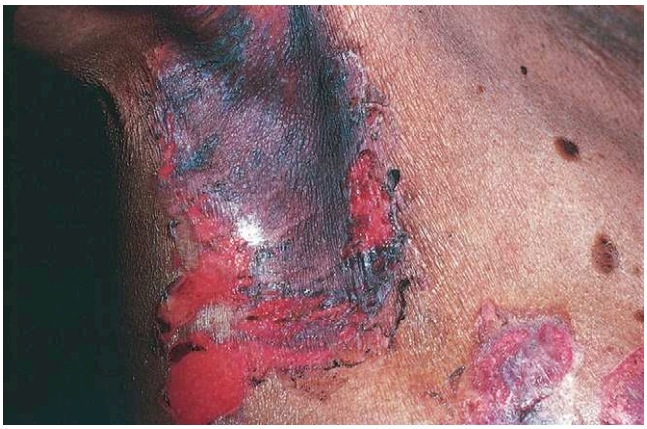


FIGURE 13-9 ■ Pemphigus vulgaris. (From Kumar V, Abbas AK, Fausto N, eds: *Robbins and Cotran: pathologic basis of disease,* ed 7, Philadelphia, 2005, Saunders.)

conjunctival blisters occurs within 1 week. Most patients demonstrate autoantibodies on serum testing. Although pemphigus vulgaris is a life-threatening condition, glucocorticoid therapy has reduced mortality rates to approximately 5%.

Cicatricial Pemphigoid

Cicatricial pemphigoid is a rare, blistering skin condition that can cause scarring of the mucosal membranes and epidermis. It commonly involves the mouth and eyes, and is a chronic and progressive disorder. As the conjunctivae become eroded, symblepharon may develop and lead to entropion, corneal scarring, and blindness (Figures 13-10 and 13-11). IgG and IgA are found deposited in the epithelial basement membrane of the skin lesions. Immunosuppressive agents are necessary in the treatment of chronic cases of cicatricial pemphigoid. Topical glucocorticoids act to control ocular scarring.

Mooren's Ulcer

This ulcer of the cornea causes a marked marginal corneal degeneration and is known as peripheral corneal melting syndrome. The cause of Mooren's ulcer remains unknown but is suspected to be autoimmune in nature. Slit-lamp evaluation of the early ulcer reveals a gray peripheral infiltrate that progresses to a circular furrow (Figure 13-12). Once diagnosed, the ulcer must be treated surgically.

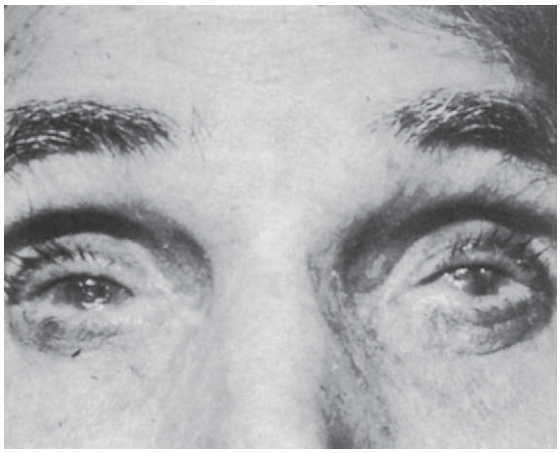


FIGURE 13-10 ■ Bullous dermatosis in cicatricial pemphigoid. (From Bietta G: Eye involvement in skin diseases. In Mausolf FA, ed: *The eye and systemic disease,* St Louis, 1975, Mosby-Year Book.)

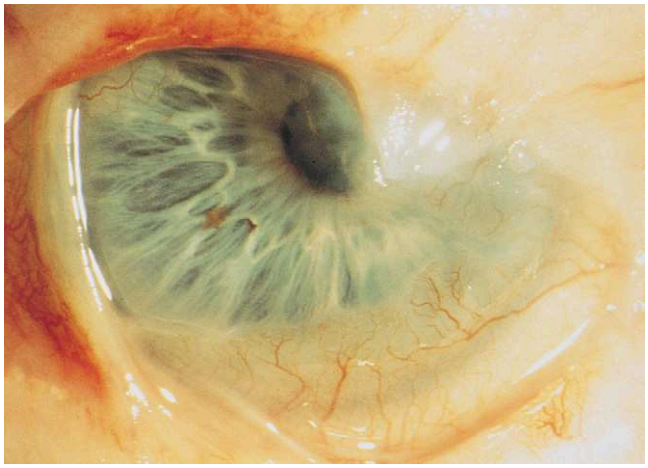


FIGURE 13-11 ■ Cicatricial pemphigoid. Lower and upper lids to the cornea in cicatricial pemphigoid. (From Yanoff M: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.)

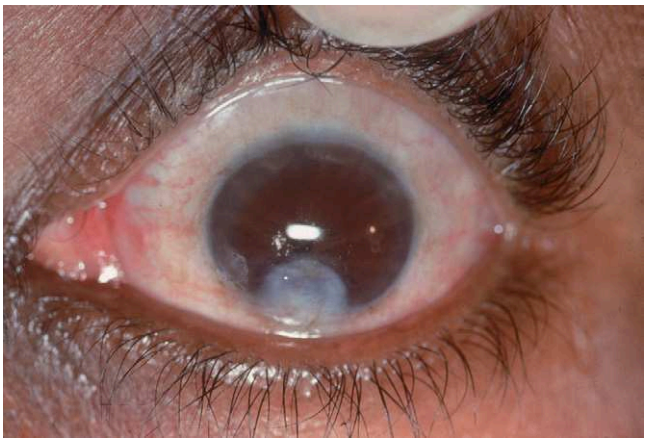


FIGURE 13-12 ■ Mooren's ulcer: Peripheral corneal melting syndrome

Type III Hypersensitivity: Clinicopathologic Correlates

Erythema Multiforme

Also known as Stevens-Johnson Syndrome (SJS), erythema multiforme has many causes, including reactions to infection and medications. Most common in men younger than 30 years, the disease's onset is heralded by fever, malaise, anorexia, headache, and nausea. This prodrome is followed by skin eruptions, most commonly on the soles of the feet and palms of the hand (Figure 13-13). The lesion is typically a "bulls-eye" lesion with a red center surrounded by a ring of normal tissue. Around this lesion is often another erythematous ring. The most common sites affected are the mucosal membranes of the nose, mouth, and eyes (Figure 13-14). The conjunctivitis is characterized by a pseudomembrane formation that forms rapidly. The conjunctiva forms blisters that break and scar, causing symblepharon, entropion, trichiasis, corneal scarring, and blindness. Treatment includes identification and immediate withdrawal of the offending agent. Aggressive management of the dry eye complications of SJS is necessary to prevent corneal involvement.

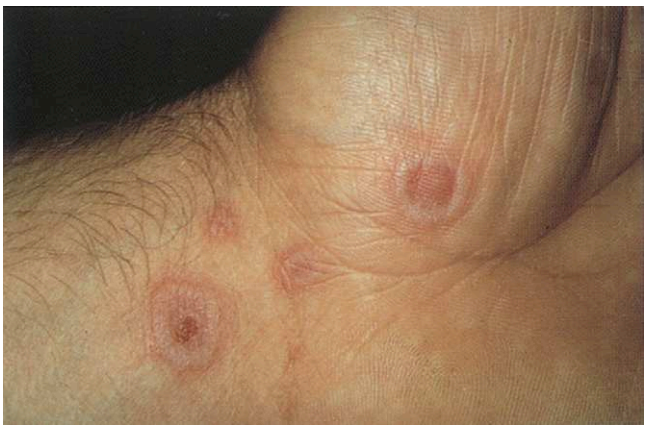
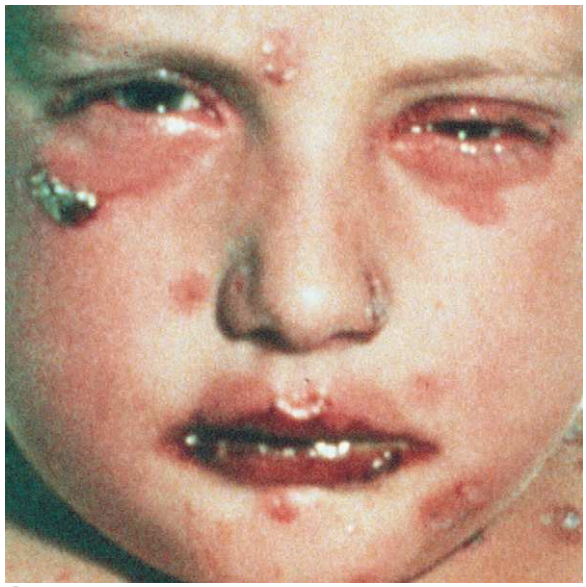


FIGURE 13-13 ■ Erythema multiforme. Note the red "bulls-eye" lesions with a surrounding pale white ring, typically found on the palms and soles. (From Goldman L, Ausiello D: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.)



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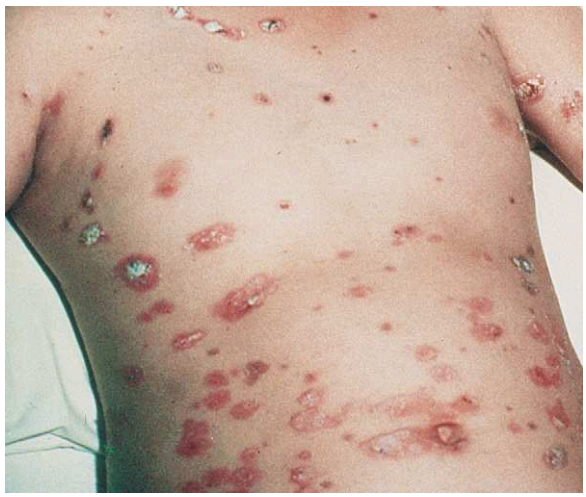

B

FIGURE 13-14 ■ Erythema multiforme: Acute phase of Stevens-Johnson syndrome. This child has the typical target shaped macular skin lesions. **A,** The head, with an associated blepharoconjunctivitis. **B,** The trunk. (From Yanoff M: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.)

Type IV Hypersensitivity: Clinicopathologic Correlates

These hypersensitivity reactions are initiated by monocytes and mediated by T cells and macrophages. These reactions are useful as a mechanism against fungi, parasites, mycobacteria, and intercellular pathogens. Unfortunately, they also mediate transplant rejection and tumor immunosuppression. The result of T-cell dysfunction, as in HIV/AIDS, causes proliferation of

opportunistic infections that result in undesirable consequences, including contact dermatitis (poison ivy), allograft rejection, granulomatous disease (sarcoidosis and Crohn's disease), and other environmentally influenced and autoimmune reactions.

Phlyctenular Conjunctivitis

This condition, also known as phlyctenulosis, causes the deposition of immune complexes in the limbus, cornea, or conjunctiva. The cause is most likely bacterial immunogens, which are antigenic and cause a delayed hypersensitivity reaction. The most common bacterial antigen in the world is the tubercle bacillus, although other bacteria have been implicated in the disease. In fact, the most common phlyctenular-associated bacterial infection in the United States is *Staphylococcus.* The lesion is a raised nodule surrounded by perivascular inflammation that causes pain, tearing, and photophobia (Figure 13-15). The eye is often red and irritated. Slit-lamp biomicroscopy will reveal a small, elevated yellowish-gray nodule on the bulbar conjunctiva or corneal limbus. During a 2-week period, the nodule will form, ulcerate, and resolve with scarring of the cornea. Clinicians should evaluate all patients with phlyctenular keratoconjunctivitis for tuberculosis by first asking the patient about any recent bouts of coughing. Ancillary tests include a skin purified protein derivative (PPD) or Mantoux test to rule out TB. Once diagnosed, the underlying disease must be treated. Topical steroids are used to treat the phlyctenular conjunctivitis.

Corneal Graft Rejection

After penetrating keratoplasty for corneal transplantation, the host immune system may recognize the foreign antigen present in the donor cornea. The rejection reaction may occur in the stroma, epithelium, or endothelium. Rejection by the immune system may lead to graft failure. Most rejection occurs between 1 month and 1 year after the procedure. Symptoms include foreign body sensation (epithelial rejection) and decreased vision with redness (endothelial rejection). Slit-lamp biomicroscopy reveals conjunctival injection, vascularization of the host peripheral cornea, microcystic edema of the wound site, and bullae formation of the cornea. To control graft rejection, topical corticosteroids are used hourly at first. Massive rejection is an indication for oral steroid use. Topical cyclosporine A (Restasis) has beneficial effects without undesirable side effects.

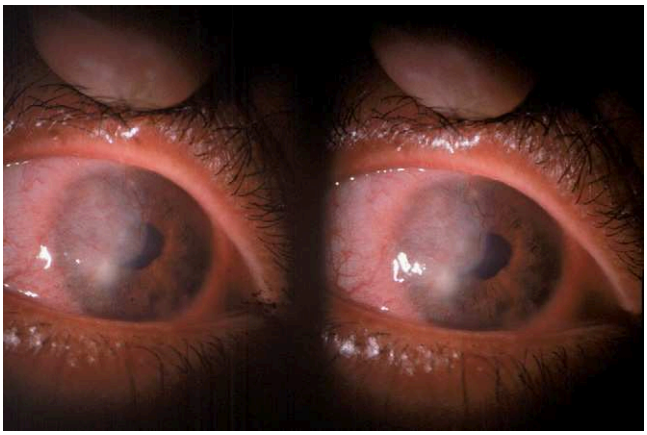

FIGURE 13-15 ■ Phlyctenular keratoconjunctivitis. Whitish, heaped-up areas along the limbus represent a sterile inflammation associated with a cell-mediated hypersensitivity response to an antigen.

AUTOIMMUNE COLLAGEN-VASCULAR DISEASE

The immune system must be able to recognize self from nonself, and most animals do not mount an immune response to host antigens. In this way, the immune system is tolerant of self-molecules. The breakdown of the basic mechanisms that control immune tolerance is known as autoimmunity. The resultant pathological disorders of autoimmunity are known as autoimmune diseases. The essential characteristic of autoimmune disease is the development of an immune response by the organism against host tissue. Autoimmunity can be idiopathic or can occur as a consequence of trauma, infection, or exposure to environmental antigens. For example, the activation of lymphocytes against host tissue may occur because of exposure to microbes in a process known as cross-reactivity.

Typical of autoimmune disease is the presence of pathological lesions that are disseminated throughout several organs and tissues. For example, systemic lupus erythematosus (SLE) manifests in the skin, joints, kidneys, and blood vessels.

As a group, collagen-vascular diseases are characterized by deposition of fibrin and diffuse inflammatory damage to connective tissue and the vascular system. In addition, some element of autoimmunity appears to play a role in these conditions. Collagen-vascular diseases often affect connective tissue, or those elements of the body that include collagen and elastin. The term collagen-vascular disease is used extensively, but it poorly describes the nature of this diverse group of clinical entities. The following collagen-vascular diseases represent the significant autoimmune disorders that affect the body and eye.

Collagen Vascular Diseases: Clinicopathologic Correlates

Systemic Lupus Erythematosus

A disease of unknown etiology, SLE is characterized by pathogenic antibodies that attack cells and tissues throughout the body. Of all cases, 90% occur in women of child-bearing age, but individuals of all ages can

be affected. Multiple organ systems are involved as autoantibodies, including T and B lymphocytes and immune complexes, cause damage by direct binding to cell membranes. A genetic predisposition to the disease appears to exist, in which some environmental influence triggers the immune response.

The American Academy of Rheumatology has developed a set of diagnostic criteria by which the presence of SLE can be established (the patient must meet 4 of the 11 criteria). These criteria include anemia, pericarditis, diarrhea, cognitive dysfunction, vascular thrombosis, musculoskeletal arthralgias and myalgias, proteinuria that indicates glomerulonephritis, and a "butterfly" rash across the bridge of the nose (Figure 13-16).

Ocular signs of SLE include retinal vasculitis, conjunctivitis, episcleritis, keratitis sicca, and optic neuritis. The retinal vasculitis of SLE appears as sheathed, narrow retinal arterioles and white exudates adjacent to the retinal blood vessels. The vasculitis is potentially blinding and must be treated with aggressive immunosuppression.

Laboratory diagnosis of SLE is made by establishing the presence of antibodies. ANA is the best screening test for SLE, though it is not specific for the disease. Serum testing may confirm the presence of anemia, leucopenia and thrombocytopenia. A Westergren erythrocyte sedimentation rate correlates with the activity of SLE. Urinalysis can be performed to measure creatinine levels, and proteinuria will reflect active nephritis.

No cure exists for SLE and the management of the condition is both complex and frustrating. Control of acute flare-ups is a primary goal of SLE therapeusis, and involves the use of NSAIDs in mild, nonlife-threatening episodes. These antiinflammatory medications will help control the potentially disabling pain and fatigue of the fever, arthralgias, arthritis, and myalgias. Systemic antimalarial medications may be used to control the SLE-associated skin lesions. High doses of glucocorticoids may be needed to control the life-threatening complications of SLE.

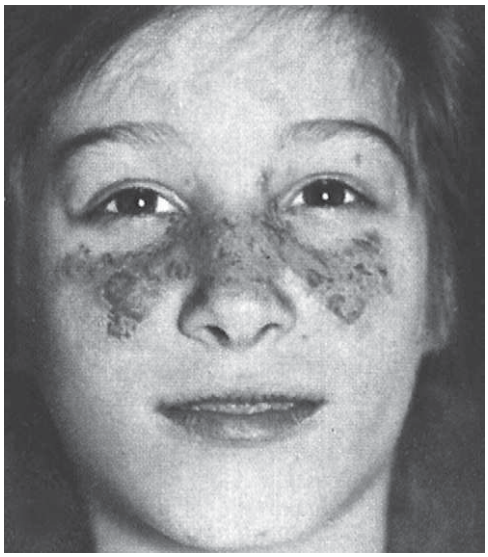

FIGURE 13-16 ■ Systemic lupus erythematosus of the face. Note the reddish "butterfly" rash across the cheek. (From Behrman RE, Kliegman RM, Jenson HB: *Nelson textbook of pediatrics,* ed 17, Philadelphia, 2004, Saunders.)

Treatment of the ocular complications of SLE includes the maintenance of the ocular surface and stabilization of the tear film, and frequent eye examinations to monitor for signs of retinal vasculitis.

Rheumatoid Arthritis

This chronic multisystem disease is characterized by inflammatory synovitis, or swelling of the peripheral joints. Relentless progressive polyarthritis may eventually result in cartilage damage and subsequent joint destruction.

The etiology of rheumatoid arthritis (RA) is unknown, but it is theorized that an environmental influence, such as a bacterial infection, stimulates the production of immune products that respond to components of the joint. Another possibility is that deposition of infective products in the synovial tissues occurs, leading to chronic inflammation of the joint.

The earliest lesions to occur in RA appear to be microvascular damage and an increase in synovial cells, but the initial stimulation for this change is as yet unknown. T cells are found in the synoveal fluids as the joint becomes edematous. This rheumatoid synovial fluid is composed of secreted products of the activated inflammatory cells and accounts for many of the clinical manifestations of RA. Within this fluid, immune complexes activate, complement, and generate chemotactic factors. In addition, mast cells will produce histamine that facilitates inflammatory cell exudation into the synovial fluid. Hyperplasia of the cells that line the joint is present. These factors produce the clinical characteristics of RA including exacerbations, remissions, variability of presentation, and chronicity.

RA begins insidiously, with the earliest symptoms of fatigue, anorexia, and multijoint involvement. During weeks to months a symmetrical involvement of the hands, wrists, knees, and feet occurs. These joints become painful, tender, and swollen, and movement becomes difficult. Patients often complain of joint stiffness during periods of inactivity and in the morning after awakening. The joints are swollen with synovial fluid and feel warm to the touch. With chronic involvement the joints become permanently damaged and there are functional changes in the feet, hands, wrists and knees.

RA can also cause the formation of nodules on the skin and meninges. Vasculitis may occur in severe RA and are associated with high titers of circulating

rheumatoid factor. Other organ involvements include the lungs, heart, and eye (Figures 13-17 and 13-18).

Almost one fifth of all RA patients develop Sjögren's syndrome and keratitis sicca. All RA patients should be followed up twice yearly for signs and symptoms of dry eye. Less than 1% of individuals with RA exhibit other ocular manifestations of the disease. Episcleritis and scleritis (Figure 13-19) are the most common ocular manifestations of RA, and the lesions resemble the granulomatous RA nodule.

Laboratory analysis helps confirm the diagnosis of RA by the use of rheumatoid factor (RF), which are autoantibodies reactive with IgG. The presence of RF is not specific for RA because it is found in the normal population, increases with age, and may be elevated in patients with SLE, Sjögren's syndrome, liver disease, sarcoidosis, TB, and hepatitis. RF is a poor screening test for RA, but high titers of RF in patients with RA indicates a prognosis of significant severity and a chronic course. Active RA elevates the erythrocyte sedimentation rate (ESR) and C-reactive protein in all cases and is prognostic for the course and severity of the disease. Radiographic analysis is helpful later in the disease, but the patterns of involvement are not diagnostic of RA.

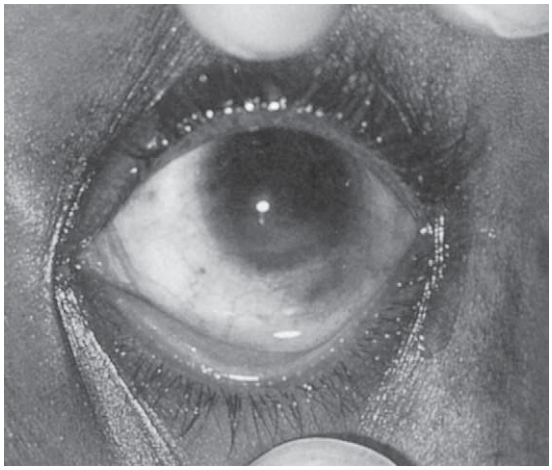

FIGURE 13-17 ■ Scleromalacia perforans secondary to rheumatoid arthritis. Note the dark gray uvea protruding through the sclera surrounded by the deep scleral injection, indicating scleritis.

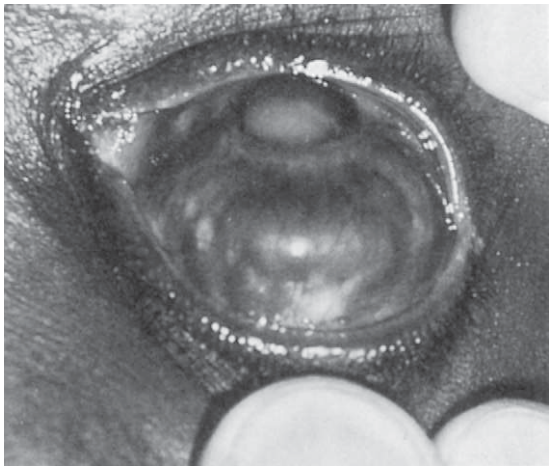

FIGURE 13-18 ■ Advanced scleromalacia perforans. Note dramatic protrusion of the uvea through a thinned-out sclera.

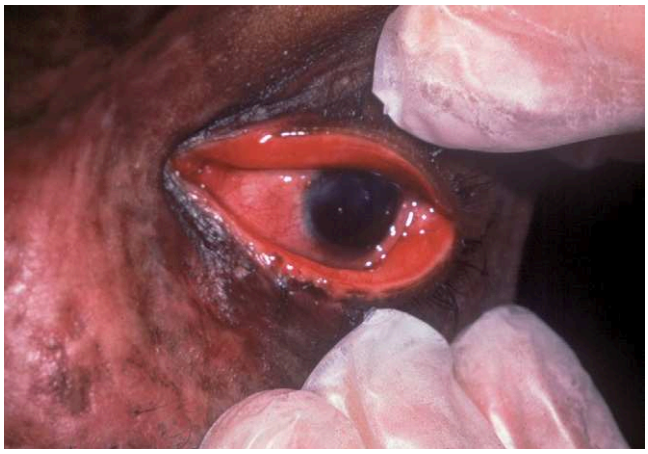

FIGURE 13-19 ■ Scleritis. Note the deep involvement of scleral vessels with reddish-blue conjunctival injection pattern.

Diagnosis of the disease is usually made by the presence of morning stiffness, symmetric arthritis of the hands or three or more joints, the presence of rheumatoid nodules, elevated RF and radiographic changes of the distal joints.

Therapy for RA aims to reduce inflammation, relieve pain, maintain the functioning of the joint, and control systemic involvement. NSAIDs and simple analgesics are used to control pain and inflammation of the joint. Methotrexate, gold compounds, D-penicillamine, the antimalarials, and sulfasalazine have all been shown to improve the course of RA. In addition, systemic steroids can provide symptomatic relief in low doses and prevent bone erosions. Immunosuppressive agents such as azathioprine and cyclosporine have been shown to be effective in the treatment of RA.

Sjögren's Syndrome

This chronic, multisystem, slowly progressing, autoimmune disease primarily affects the eyes, mouth, and throat. A lymphocytic infiltration of the exocrine glands, Sjögren's syndrome causes dry eyes, nose, and mouth. It affects mostly middle-aged women and can occur either in isolation or in association with systemic diseases such as RA. The disease is characterized by B-lymphocyte hyperreactivity and circulating autoantibodies. Lab testing of patients with Sjögren's syndrome often reveals elevated RF and assorted antigens.

In general, lacrimal and salivary gland function are diminished, with consequential mucosal dryness. In the mouth and throat, atrophy of the tongue and reduced

salivary secretion are present. Patients will complain of difficulty swallowing food and speaking.

In the eyes, destruction of the corneal and bulbar conjunctival epithelium occurs, causing the symptoms of dry eye, including sandy, dry, or gritty ocular sensations. The conjunctiva becomes infected, with the development of keratitis sicca.

The symptoms associated with Sjögren's syndrome are a result of generalized dryness, or xerostomia. Besides dry mouth and eyes, exocrine involvement of the respiratory tract results in dry nose, throat, and trachea. Nosebleeds are a common sign of respiratory tract involvement. In addition, a reduced exocrine secretion in the gastrointestinal tract can lead to gastritis and pancreatitis. It is not unusual for patients to also exhibit drying of the skin.

Late in the course of the disease, parotid gland enlargement and lymphadenopathy can occur as a manifestation of low-grade lymphoma.

The ocular involvement of Sjögren's syndrome includes a reduced tear lake, punctuate epithelial keratopathy with staining, a reduced break-up time, and an associated blepharitis.

Sjögren's syndrome is an incurable disease, and treatment is aimed at symptomatic relief and control of the xerostomia of the mucosal membranes. Topical cyclosporine A (Restasis) used several times daily will help reduce the effects of keratitis sicca. The use of oral flax seed oil and omega-3 fish oil capsules has been advocated in the relief of dry eye, but control studies on these over-the-counter supplements is lacking. Patients should be advised to practice appropriate dental hygiene to reduce the risk of dental caries and gingivitis caused by drying of the mouth. Oral pilocarpine (Salagen) appears to improve sicca manifestations. Stimulation of exocrine glands with the oral agent cevimeline (Evoxac) can help relieve the symptoms of keratitis sicca and dry mouth. Glucocorticoids and cyclophosphamide help to suppress the immune system in cases in which Sjögren's syndrome involves the kidneys, lungs, and blood vessels.

Scleroderma

In scleroderma (SCC), an overproduction of collagen occurs that tends to accumulate throughout the body. The earliest involvement is the small arteries, arterioles, and capillaries of the skin, gastrointestinal (GI) tract, lungs, and heart. Injury to the endothelial cells of these small blood vessels is followed by thickening of the vessel walls. The lumen subsequently narrows and eventually the vessels obliterate. This vascular injury ultimately results in chronic ischemia to the skin and organs.

The mechanism behind the vascular injury is unknown, but it involves derangement of normal immune function. Cytotoxic factors for blood vessel endothelium cause collagen release and has been found in some patients with SCC. In addition, increased levels of macrophages and T cells are found in the lesions associated with SCC.

The earliest clinical symptom of SCC in Raynaud's phenomenon, a condition caused by ischemia to the digits and yielding blanching, cold sensations, swelling and eventual rewarming of the fingers and toes. The earlobes and tip of the nose are also sites prone to develop Raynaud's phenomenon.

Digit involvement is followed by swelling of the limbs. Telangiectasias of the skin develop on the face, fingers, lips, and tongue. The fingers and knees become stiff. Bloating and abdominal pain occur when the GI tract becomes involved. Lung involvement includes dyspnea, coughing, and pneumonia. SCC can result in heart failure, renal failure and hypothyroidism. SCC frequently causes dry eyes, and all patients seen with keratitis sicca should be queried about Raynaud's phenomenon symptoms.

Laboratory testing reveals an elevated erythrocyte sedimentation rate and anemia. In 25% of cases of SCC, the patient has an elevated RF.

Most cases are diagnosed on the basis of Raynaud's phenomenon in association with typical skin lesions (Figure 13-20). The course of the disease is highly variable.

No cure exists for SCC. Pharmacological intervention has included the use of D-penicillamine, azathioprine,

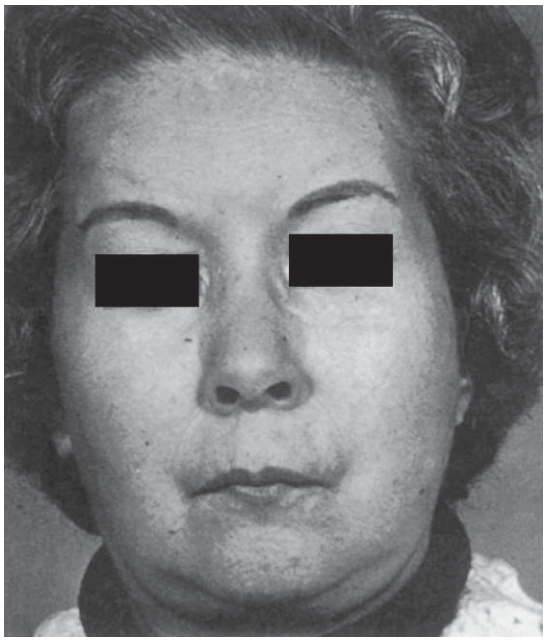

FIGURE 13-20 ■ Scleroderma. Note the classic signs of the tight skin over the forehead, nose, and cheeks, giving a "pinched" facial appearance and a reduced palpebral aperture size. (From Cawson RA, et al: *Pathology: the mechanisms of disease,* St Louis, 1989, Mosby Year-Book.)

methotrexate, cyclophosphamide, aspirin, and glucocorticoids. All of these agents have been shown to offer some benefits, but control studies are still lacking.

Ocular dryness in cases of SCC is best managed with tear substitutes. The use of oral flaxseed oil and omega-3 fish oil capsules has been advocated for the relief of dry eye, but control studies are lacking.

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is characterized by inflammation involving the distal joints and central skeleton. As one of the spondylarthropathies, AS shares with other immune disorders an association with the HLA-B27 allele. In fact, 90% of patients with AS have inherited this antigen.

In AS the ligamentous attachment to bone, or enthesis, is the primary site of involvement. Lesions are found most often in the sacroiliac joint and between the vertebrae of the spine.

The earliest manifestation of AS is sacroiliiitis. The lesions consist of lymphocytes, mast cells, and macrophages, along with bone marrow edema. New bone formation occurs within the ligamentous lesions. The joint becomes swollen and is eventually replaced by fibrocartilage. Ossification results in complete obliteration of the joint.

At least 20% of patients with AS develop an acute anterior uveitis, or iritis. The associated iritis is often an acute anterior uveitis with formation of a plasmoid aqueous and hypopyon. The pupil may be secluded by an immune membrane. The iritis may be the first clinical sign heralding the presence of AS.

The cause of AS is unknown, but it is thought that the inherited HLA-B27 allele predisposes the patient to develop the inflammation because of exposure to an environmental stimulus, most likely an enteric bacteria.

AS occurs most often in the years from the late teens to age 30, with a median patient age of 23 years. Women are affected slightly more often than men.

The earliest symptom is an intermittent, dull, lower back pain that is worse in the morning. The morning stiffness can last a few hours. Within months the pain becomes constant and boring.

AS has a variable course and patients can have mild, persistent lower back pain with minimal complications, or total fusion of the vertebrae known as "bamboo spine." Spinal fractures may occur with even minor trauma. The posture of the patient becomes hunched-over and rigid.

Laboratory testing for AS can reveal the presence of the HLA-B27 allele, elevated sedimentation rate, and C-reactive protein. Elevated alkaline phosphatase occurs in severe cases of AS, and RF and antinuclear antibody tests (ANA) are typically negative. Radioimaging reveals sacroiilitis and other joint involvement.

Treatment of AS aims to maintain good posture, mobility, and motility, provide for a significant range of motion, and reduce pain. To this end, exercise, hot baths, massage therapy, and smoking cessation have all led to an improved lifestyle for patients with AS. Symptomatic relief can be achieved by use of antiinflammatory medications. Oral NSAIDs may reduce morning stiffness, and glucocorticoid injections into the sacroiliac joint provide temporary pain relief.

Treatment of AS-associated iritis makes use of topical steroids and cycloplegic agents, with topical phenylephrine for breaking posterior synechiae or secluded pupil.

Reactive Arthritis

Once known as Reiter's syndrome, reactive arthritis (ReA) demonstrates the classic constellation of signs including arthritis, urethritis, and conjunctivitis. Mucocutaneous lesions are also associated with the classic presenting signs of ReA in 78% of cases.

The arthritis typically occurs in a patient with the HLA-B27 allele and follows infection by, for example, salmonellae or chlamydiae. ReA occurs in patients in the age range from 18 to 40 years, and is seen equally in men and women.

ReA is an inflammatory arthropathy with lesion formation similar to AS. It is believed, but has yet to be proven, that intracellular bacteria are protected by the HLA-B27 allele, and that this permits infected white blood cells to migrate to the joints in which the arthritis occurs because of a T cell response to the bacterial antigens.

The clinical features of ReA are highly variable, but a thorough history usually reveals a significant infection 1 week to 1 month before the onset of symptoms. At first, the patient experiences fatigue, malaise, weight loss, and fevers. The arthritis is acute in onset, and a new joint is involved every 1 to 2 weeks. The peripheral joints, including the knees, ankles, wrists, and fingers, are most often affected. The joint involvement may reoccur and cause persistent and incapacitating pain.

An accompanying urethritis (urinary tract infection) with symptoms of urinary urgency and increased urination frequency is often associated with the arthritis. A genitourinary discharge may also be present.

Other systemic associations include skin lesions on the palms (Figure 13-21) and soles, genital ulcers, oral ulcers, and heart and lung complications.

An acute plastic iritis may be associated with ReA, and can be refractory to treatment. Even with appropriate and aggressive treatment, subsequent corneal meltdown can occur that leads to blindness.

Laboratory findings will reveal an elevated erythrocyte sedimentation rate, mild anemia, a positive

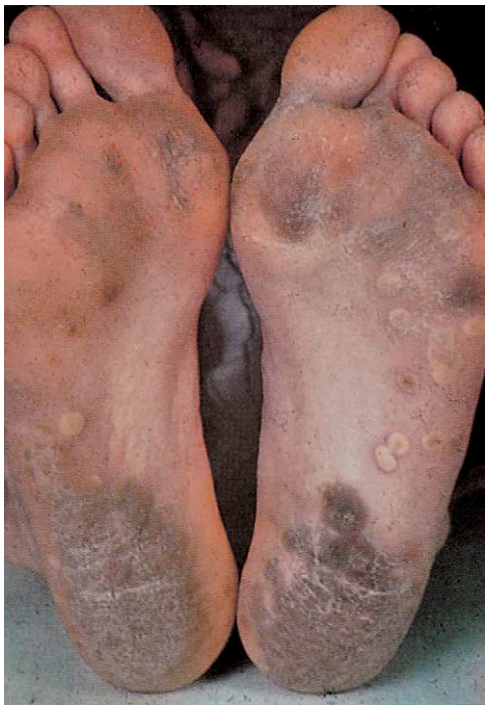

FIGURE 13-21 ■ Keratoderma blennorrhagicum. Hyperkeratotic lesions of the foot in Reiter's syndrome. (From Goldman L, Ausiello D: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.)

HLA-B27 allele in approximately 75% of ReA cases, and radiographic confirmation of joint involvement.

The goal of ReA treatment is the relief of pain, and this is often accomplished by the use of NSAIDs. In general, glucocorticoids are avoided in cases of ReA unless the patient is confined to bed. Antibiotics have not been shown to play a role in the treatment of ReA. ReA caused by chlamydial infection should be treated with oral azithromycin 1000 mg for 1 day, and all sexual partners should be contacted for treatment. As with AS, physical therapy and exercise are encouraged to strengthen the muscles to the involved joints.

VASCULAR AUTOIMMUNE DISEASE

Inflammation and damage to the blood vessels characterizes vascular autoimmune disease, or vasculitis. Typically, narrowing or obliteration of the vessel lumen and consequential ischemia to tissues downstream occurs. The immune system appears to mediate the damage, to some extent, in almost all cases of vasculitis. A deposition of immune complexes into the blood vessel wall occurs in vasculitis. The antigen that stimulates the immune response has not been identified in most cases, although hepatitis B immunogen has been identified in patients with polyarteritis nodosa (Figure 13-22).

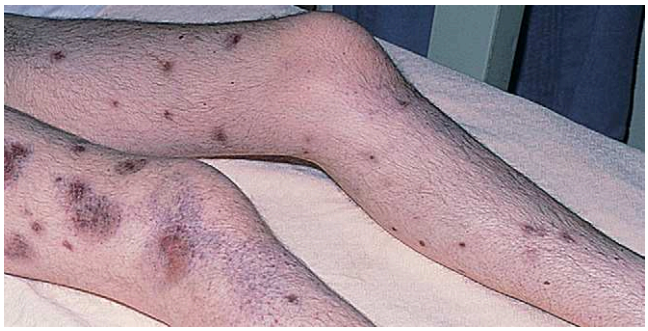

FIGURE 13-22 ■ Polyarteritis nodosa. Chronic painful ulceration of the leg, ankle, and foot in a patient with polyarteritis nodosa. (From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.)

Wegener's Granulomatosis

This vasculitis of the upper and lower respiratory tract is characterized by granulomatous deposition within the small arteries and veins. The kidneys may also be involved. Typical symptoms include nosebleeds with sinus pain, ear pain, skin lesions, and coughing.

In 50% of cases of Wegener's granulomatosis ocular involvement exists, including conjunctivitis, dacryocystitis, episcleritis, and proptosis. An associated granulomatous uveitis with mutton-fat keratic precipitates may be present

Laboratory testing will reveal an elevated ESR, anemia, elevated RF, and thrombocytosis.

Although once incurable and fatal in all cases, Wegener's granulomatosis is now treated with cyclophosphamide for 1 year combined with oral glucocorticoids during the first 6 months of treatment. This treatment results in complete remission in 75% of cases. Approximately 50% of remission cases relapse eventually, and although these cases are again treated, permanent complications increase, including renal insufficiency, hearing loss, and throat scarring. Azathioprine may help maintain remission.

Temporal Arteritis

Also known as giant cell arteritis (GCA) or cranial arteritis, this vasculitis is characterized by inflammation of the medium- and large-sized arteries throughout the body. The most commonly affected sites include the branches of the carotid artery, especially the temporal artery (Figure 13-23). One of the most serious complications of GCA is a profound vision loss that is the result of arteritic ischemic optic neuropathy.

Typical of autoimmune vasculitis, the arterial walls become thickened by granulomatous deposition and giant cell formation and infiltration resulting in luminal narrowing. Obliteration of the lumen will result in ischemia of downstream tissues.

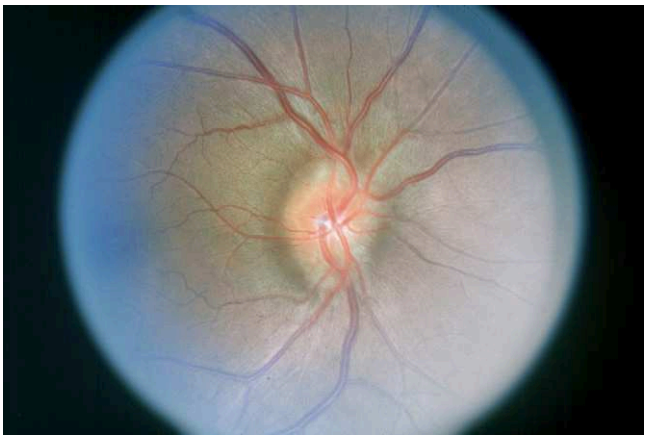

FIGURE 13-23 ■ Swelling of the optic nerve head in a patient with temporal arteritis.

GCA is found most often in the Scandinavian populations around the world. The disease is more common in women than in men and tends to be rare in blacks. There is an association with the HLA-DR4 allele. GCA occurs most often in patients older than 55 years and is most common in the elderly population of patients 70 years and older.

Systemic involvement of the extracranial arteries, the aorta, subclavian arteries, and coronary arteries lead to the systemic manifestations of GCA. These symptoms include fever, anemia, headaches, malaise, anorexia, and bodywide muscle pain.

Involvement of the temporal artery causes headache and a thickened, palpable, and tender temporal artery. Pain of the scalp upon palpation or chewing may occur. These symptoms can occur for months before vision is affected.

The most feared complication of GCA is ischemic optic neuropathy with subsequent vision loss. The vision loss is usually unilateral and is often accompanied by headache. Other systemic findings on examination for visual loss include a palpable, nodular, and tender temporal artery, fever, malaise, diffuse joint or muscular pain, and pain on chewing.

Ocular work-up of a unilateral case of temporal arteritis usually begins when the elderly patient is seen for an emergency examination with a sudden onset of vision loss and headache. Visual acuities may be reduced to 20/400 or worse in the involved eye. A relative afferent pupillary defect (RAPD), or Marcus Gunn pupil, will be present in the involved eye. Fundus evaluation may reveal a pale, swollen disc (disc edema), or a central retinal artery occlusion (CRAO). Visual fields reveal a classic altitudinal visual field defect in the involved eye.

Laboratory testing must be instituted on an emergency (stat) basis. Lab findings include an elevated erythrocyte sedimentation rate (by Westergren technique) and C-reactive protein. The diagnosis of GCA is confirmed by temporal artery biopsy with serial sectioning of the vessel so that inflamed areas are not missed.

The treatment of a suspected case of GCA should not wait until biopsy confirmation of the condition. The goal of treatment is to reduce the risk of contralateral temporal artery involvement and vision loss in the uninvolved eye. If the condition is strongly suggested by vision loss, temporal artery tenderness, headache, and disc edema, then treatment should be instituted and continued even if the biopsy results are normal. GCA is amenable to glucocorticoid therapy. Oral prednisone is begun at 60 to 120 mg per day for 1 month, followed by a taper to a maintenance dose of 10 mg per day. Some studies suggest that for the first 5 days, 1 gram of intravenous methylprednisolone should be given daily, and then oral glucocorticoids should be started on the sixth day. Treatment should continue for 1 to 2 years. The ESR and C-reactive protein are used to monitor the effectiveness of the treatment and help to determine the appropriate tapering schedule.

INFLAMMATORY AUTOIMMUNE DISEASE

Autoimmune disease may affect various organ tissues throughout the body. In most cases the causes remain unknown, but an exaggerated immune response to an unknown antigen is usually present.

Sarcoidosis

This multisystem, granulomatous disease is characterized by the accumulation of T cells and phagocytes in otherwise normal tissue. The cause of the condition is unknown, but a definite immune response is present to an as yet unknown antigen. The most common site of inflammation is the lung, thus it is believed that the antigen is inhaled.

This common disease affects males and females equally and occurs in all age ranges, although it is most commonly found in patients between the ages of 20 and 40 years. All races are affected, although in the United States the condition is more frequent in blacks. Despite the lung involvement, the condition is more common in nonsmokers.

The most common site of involvement is the respiratory tract and the most frequent presenting symptom is a cough. Early systemic manifestations include fever, malaise, fatigue, and anorexia. Other organ systems that commonly are involved include the lymph nodes, skin, liver, and eyes.

In the lung, the inflammation involves the alveoli, bronchi, and small blood vessels. Dyspnea can occur with exercise and is accompanied by a dry cough.

Lymphadenopathy occurs in 90% of sarcoid cases. Approximately one quarter of individuals with sarcoid develop skin problems, including erythema nodosum, nodules, and plaques.

Approximately 25% of individuals with sarcoidosis have ocular involvement. Granulomatous lesions may be found on the corneal endothelium iris and choroids. Sarcoid nodules may infiltrate the optic nerve, causing a mechanically induced or toxic optic neuropathy with disc edema. Sarcoid nodule deposition in the brain can cause an elevation of cerebral spinal fluid that induces papilledema. Of patients with sarcoid-induced ocular involvement, three quarters have anterior uveitis. The intraocular inflammation is typically anterior, granulomatous, and chronic in nature. The onset is insidious, and often the patients are unaware of any eye problems until a slit-lamp evaluation reveals cells in the anterior chamber. Chronic uveitis associated with sarcoidosis can cause retinal vasculitis, resulting in a sheathing of peripheral retinal arterioles that resembles "candle-wax drippings." Treatment of the anterior uveitis in cases of sarcoid involves topical cycloplegic agents and topical steroid eye drops.

Laboratory testing in sarcoidosis reveals an elevated ESR and angiotensin-converting enzyme (ACE). In fact, ACE is elevated in 66% of sarcoid cases, but remains nonspecific for the disease. Hypercalcemia occurs in 25% of individuals with sarcoidosis. Radiography reveals abnormal lung fields, with either bilateral hilar adenopathy or diffuse parenchymal changes.

Sarcoidosis is most commonly diagnosed by combining the symptomology, most often a dry cough, with radiographic evidence of lung involvement. Laboratory testing is nonspecific for sarcoid, and skin allergy tests are not diagnostic of the disease. A transbronchial biopsy to obtain a sample of the lung parenchyma is mandatory to make a definitive diagnosis of sarcoidosis.

The course of the disease is variable and the prognosis is good, with 50% of cases resolving spontaneously with no treatment or sequelae. Many cases go undiagnosed because of mild symptoms and signs.

Oral glucocorticoids are mandatory in the treatment of sarcoidosis. Steroids suppress the T lymphocyte inflammation at the site of the sarcoid lesion. The usual therapeutic regimen involves the use of oral prednisone for 4 to 6 weeks, followed by a slow taper during the next 3 months.

MUSCULOSKELETAL AND JOINT AUTOIMMUNE DISEASE

Osteoarthritis

This, the most common disease of the joints, increases in frequency with age. Osteoarthritis (OA) is heavily influenced by use during the lifetime of the patient, and repeated trauma to the joints exacerbates a strong risk factor. Except for trauma, however, no exercise activity has been related to the development of OA, including long-distance running or jogging. Obesity plays a role in the development of knee OA.

OA is a disease of the synovial joint, in which a progressive loss of articular cartilage occurs. Early in the course of the disease, thickening of the cartilage in the load-bearing joints occurs. With time, the joint tissue thins and the thickened cartilage softens. Fibrocartilaginous replacement of damaged cartilage cannot hold up to constant load-bearing movement, and eventually the bones of the joint hypertrophy and become remodeled.

OA occurs as the result of two mechanisms: either the tissues of the joint fail because of excessive load or the cartilage or bone tissues become deranged. The earliest modification of the tissues in OA begins in the cartilage because of a change in the arrangement and size of the cartilage fibers. A defect in the collagen matrix becomes apparent, and the substance that binds the collagen fibers together begins to fail. At the core of this loss of collagen support are lysozymal enzymes that dissolve the "glue" that provides adherence of adjacent collagen fibers. Cartilage temporarily thickens when the collagen is disrupted to compensate for the loss of joint integrity, but eventually OA is characterized by chronic cartilage loss.

The clinical symptoms of OA consist of a deep, boring ache of the involved joints and stiffness of the joints in the morning. The pain of OA may be the result of such causes as inflammation of the synovium or joint capsule, spasm of the adjacent muscle, microfractures of the bones, stretching of the periosteal nerve endings, and stretching of the ligaments. The joint may be tender on palpation and swollen when inspected.

Radiography is useful in the diagnosis of OA. The joint space is seen to be narrowed, and the contour of the joint is modified. The joints most often involved in OA are the fingers, hip, knee, and spine, and each demonstrates specific changes visualized on radiographic analysis. Laboratory testing remains insensitive and nonspecific for OA.

The treatment of OA has three goals: minimizing disability, maintaining mobility, and reducing pain. Therapy begins with an analysis of body mechanics, with the goal the correction of poor posture to ameliorate ineffective load bearing. Reduction of joint stress may be achieved by reducing obesity, use of a cane during walking or standing, redistribution of load-bearing tasks, frequent rest periods, and podiatric evaluation of foot and shoe integration. Physical therapy, heat application to the involved joints, and appropriate exercise can all help alleviate the complications of OA.

OA can not be prevented by drug therapy, but the appropriate use of medications can help alleviate the pain associated with joint disease. The use of NSAIDs can improve mobility and decrease joint pain, but significant GI side effects limit the chronic use of these pharmaceuticals. The use of COX-2 inhibitors to reduce OA pain is currently under scrutiny and remains controversial because of studies that link these medications to an increased risk of cardiovascular events and stroke. Glucocorticoids are of no benefit in cases of OA. In most cases of OA, acetaminophen is prescribed for joint symptoms. In cases of advanced OA, orthopedic surgery may be used for joint replacement.

Gout and Gouty Arthritis

Inflammation of the joints may occur as the result of deposition of monosodium urate crystals in the synovial fluid. These crystals take on the form of needles and rods. Their presence in the involved joint or joints may cause the acute or chronic arthritis known as gout. Gout most often occurs in middle-aged to elderly men, and begins in one joint, usually the big toe (i.e., the metatarsophalangeal joint). Gout will often spread to involve the ankles and knees and, in the elderly, the fingers. The acute episode of arthritis causes joint pain, swelling, and tenderness, with resolution in 3 to 10 days. Known as gouty arthritis, the condition is exacerbated by dietary, iatrogenic, and traumatic factors, among others.

Needle aspiration of the synovial fluid will confirm the presence of urate crystals, thus confirming the diagnosis of gout.

Acute gout is treated with NSAIDs or glucocorticoids. Long-term therapy for the control of serum uric acid levels involves weight loss, a low-purine diet, increased fluid intake, and the use of uricosuric agents. One preferred uricosuric agent used to lower urate formation and prevent stone formation is allopurinol.

In patients with gout, urate crystals may deposit in the eye in the corneal stroma. This deposition causes corneal clouding with subsequent visual blurring and a foreign body sensation. The cornea appears hazy, and the deposition is grayish-white and located centrally. Treatment consists of corneal epithelial debridement with removal of the urate crystals with a chelating agent such as EDTA. The cornea may also develop a band-shaped keratopathy because of the deposition of yellow, retractile crystals near Bowman's membrane.

Other ocular complications of gout include the deposition of conjunctival nodules in the interpalpebral space and often associated with a marginal keratitis. In addition, gout has been associated rarely with anterior uveitis, scleritis, and cataract. Nodules called tophi that bear uric acid crystals can be found in the eyelids of patients with gout.

Fibromyalgia

Characterized by generalized musculoskeletal pain and joint stiffness, fibromyalgia primarily affects women, who are diagnosed 9 times more often than men. Almost 4% of all women in the United States have symptoms of fibromyalgia, which occurs most often in women older than 50 years. The pain and stiffness associated with fibromyalgia occur without any inflammation, and no associated muscle or joint pathology has yet been discovered. Often associated psychiatric disturbances are present, including depression and anxiety. It is unknown whether the pain of fibromyalgia causes the psychiatric condition, or if an underlying mental health issue contributes to the sensation of muscle pain.

Fibromyalgia and chronic fatigue syndrome share many common characteristics, including fatigue, poor sleeping habits, musculoskeletal pain, and depression. Chronic fatigue syndrome often appears abruptly, is often associated with viral symptoms, and does not have as many palpable tender musculoskeletal points as does fibromyalgia, however.

Adjunctive treatment of fibromyalgia includes patient education, heat, massage, exercise, acupuncture, and hypnotherapy. Pharmaceutical intervention includes tricyclics (such as amitriptyline), antidepressants, and antianxiety medications.

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CHAPTER 14

Infectious Disease

CHAPTER OUTLINE

VIRAL INFECTIONS

Viruses are parasites, composed of nucleic acid and surrounded by protein, that require cells to replicate. Their compositional nucleic acids are necessary to replicate and produce new viral particles within host cells. Viruses do not contain certain elements necessary for sustaining life, however, such as enzymes or ribosomes. Viruses cannot metabolize lipid, carbohydrate, or protein, and therefore depend on host cells for the elements of life.

For a virus to infect a host cell, a specific surface viral protein must bond with and fuse to a receptor molecule on the plasma membrane of the cell. Next, the virus penetrates the cytoplasm of the host cell. Inside the cell, the virus loses its protein coat and releases nucleoprotein into the cytoplasm. The virus genome is replicated inside the cell, causing assembly of protein and nucleic acid complexes. At this point, the virus exits the cell through the mechanism of bonding to and transiting through the cell membrane. During this process of "budding," the naked viral particle confiscates glycoprotein molecules to manufacture a new envelope.

The infected cell is adversely affected by viral infection because of the inhibition of vital DNA, RNA, and protein replication. The host cell can partially block or inhibit viral affects by innate host resistance factors. One such nonspecific factor is interferon, a compound produced by the cell to inhibit viral replication. Body-wide resistance to viral infection starts with physical barriers including the structure of the skin and mucous membranes, secretions (including mucous, tears, saliva, and sweat), and the release of inflammatory cells and cytokines. Within 1 week, the immune system produces a T-cell lymphocyte virus-specific antibody reaction, which persists for many months after the primary viral infection.

Viruses are most often spread by inhalation of aerosolized particles, direct physical contact, or ingestion of contaminated food or water. Viral particles gain access to the body through the mucosal linings of the nasal or respiratory tracts, the digestive system, or the genitourinary tissues. The virus spreads through the body as viral particles are carried to distant tissues through the lymphatic system, the bloodstream, and neural connections.

The initial viral infection lasts from days to weeks, and symptoms can range from subclinical characteristics to a fulminant manifestation. The initial infection stimulates both specific and nonspecific immune responses. Nonetheless, cases of persistent, chronic, and latent viral infections occur, most significantly HIV, hepatitis, rabies, measles, and herpes viruses. These chronic viral infections are estimated to cause as much as 20% of human cancer malignancies.

HIV and AIDS

Historic Perspective

In 1981, the first reports were made of patients in the United States with a disease that would eventually become known as acquired immunodeficiency syndrome (AIDS). The first human immunodeficiency virus (HIV-1) was isolated in 1983 and identified in 1984. The first antibody-detection tests were marketed in 1985, consisting of a virologic test for the diagnosis and monitoring of HIV-infected individuals.

In 1985 human immunodeficiency virus type 2 was isolated and identified the following year in patients from West Africa. HIV-1 and HIV-2 share similarities, including mode of transmission, opportunistic infection, and association with AIDS. HIV-2 infection typically causes a milder immunodeficiency, however, that is slower to develop than HIV-1. HIV-2 is found predominantly in Africa and is rare in the United States. The virus was discovered in the United States in 1987, but the prevalence has remained low, and testing for HIV-2 is not recommended in the United States.

Histopathology

The HIV virus causes a destruction of the immune system in an HIV-infected individual. The pathogenesis of HIV infection addresses the establishment of the infection and the eventual complication known as AIDS.

HIV infection causes the damage or death of the immune system, and thus the body cannot fight infections and certain cancers. The viral infection is characterized by the disabling and destruction of crucial immune cells known as "T-helper cells," or CD4 T cells. CD4 T cells play a crucial role in the immune system by coordinating the functions of other immune system cells. Therefore, the lower the number of CD4 T cells the more impaired the immune system. As the population of this cell type diminishes there is a greater risk of opportunistic infections and cancers to take hold and flourish. These infections and malignancies can arise in any system, including the eyes, lungs, intestinal tract, and neurologic system. Certain cancers, including Kaposi's sarcoma and certain lymphomas, may arise in people with AIDS, the end-stage of HIV infection.

HIV most likely causes AIDS by causing the direct destruction of CD4 T cells. This process disrupts other immune cells and thus influences the chemical mediators of the immune system. CD4 T cells are killed directly when the virus buds out of the host cell, causing lipid membrane disruption. In addition, the accumulation within the CD4 T cell of viral proteins and nucleic acids can be toxic to the cell and disrupt cellular functions. CD4 T cells may undergo programmed cellular death caused by the presence of HIV-related proteins within the cytoplasm. In addition, killer T-cells may attack any cell that has HIV particles adhering to the cell membrane, even if no active cell infection could occur. Eventually, HIV-mediated destruction of the lymph nodes leads to the immunosuppressive characteristic of AIDS.

Virology

HIV is a retrovirus that must make a DNA copy of the host cell's RNA to replicate. The DNA necessary for such replication is found within host cells, and only HIV and retroviruses use the enzyme reverse transcriptase to convert RNA to DNA for incorporation into the host cell's genes. The virus is spherical in shape with a lipid two-layered viral envelope. The virus enters the host cell through a receptor on the cell membrane composed of high amounts of cholesterol and glycolipids known as a "lipid raft."

The core of the HIV virus is a protein "capsid" that surrounds two single strands of HIV RNA. Each strand of HIV RNA contains a copy of the virus' nine genes. Only three genes (*GAG*, *POL*, and *ENV*) contain the necessary information to make proteins for new virus particles. The other six genes control HIV infection, replication, and disease production.

Infection

HIV infection occurs when a viral particle encounters a receptor site on the CD4 cell membrane. The HIV particle binds tightly to the CD4 surface receptor molecules and the virus envelope and cell membrane fuse, leading to egress. Other immune cells may be infected in this way, including monocytes and macrophages. These lymphocytes are not killed by the presence of HIV particles within them, and thus act as reservoirs of HIV.

Within the cytoplasm of the host cell, HIV reverse transcriptase is used to convert viral RNA into DNA. This new DNA is then transported to the cell nucleus, where it is spliced into the host cell's native DNA. Next, host cell RNA makes copies of the infected DNA strand. The newly modified RNA usurps the host cell's protein manufacturing process to create viral-mediated proteins. This transcription of the copied RNA, or messenger RNA (mRNA), is now controlled by the HIV genes. New mRNA is transported to the cell cytoplasm, where new viral proteins and enzymes are now manufactured by using mRNA as a template. This process of translation eventually results in a gathering of HIV core proteins, enzymes, and RNA within a new viral particle. This particle binds with the cell membrane from within the host cell, migrates through the double-lipid layer, acquires the necessary molecules for a viral envelope, and exits the cell. Once the long chains of enzymes and proteins within the viral

core are lysed by the viral enzyme protease, the virus is infectious to other cells.

Immunopathology

On a macroscopic level, HIV infection spreads quickly throughout the body and seeds numerous organs. Within 2 to 4 weeks of the initial exposure, patients experience flu-like symptoms. HIV levels are reduced by killer T cells (CD8 T cells), which are critical elements of the immune response, and B-cell–produced antibodies. As the population of HIV virus is reduced, the CD4 count may rise back to a nearly normal level. HIV-related symptoms disappear for many years, but some HIV particles escape this immune response. Most often, the lymph system, seeded during the initial infection, serves as a reservoir for the multiplying HIV virus. Early in the disease, the virus replicates actively in the lymph tissues, in which CD4 cells are activated by the release of cytokines in the immune tissues. This process allows uninfected immune cells to become easily infected, and ultimately chronic immune cell activation causes breakdown of the lymph node architecture. Fibrotic replacement of lymph tissue accelerates the destruction of the immune system.

The HIV virus most likely escapes complete obliteration by the initial immune response because of a high degree of mutation that occurs during replication. In addition, the HIV virus may hide within chromosomes of infected cells and thus be shielded from immune scrutiny. A massive replication process is characteristic of HIV infection, producing billions of new viral particles daily with a high rate of mutation caused by imprecision by the HIV enzyme reverse transcriptase during transcription.

Modes of Transmission

The most common form of HIV infection is unprotected sex with an infected partner. Because the virus can enter the body through the mucous membranes of the mouth, penis, vagina, vulva, or rectum, any form of sexual contact with a person with HIV places the individual at risk for infection. Heterosexual intercourse accounts for more than 85% of cases of HIV infection in developing counties. Homosexual intercourse accounts for an additional 5% to 10% of cases.

Other behaviors that place individuals at risk for infection with HIV include the sharing of needles and syringes, and mother-to-child transmission during pregnancy and birth.

Screening for contamination of blood products has far reduced the risk of infection by this mode of transmission, but in many developing countries blood donations remain unscreened.

Appropriate measures may be implemented to reduce the risk of HIV infection. All patients should be encouraged to use condoms for oral or genital sex with partners whose HIV history is unknown.

Intravenous drug users should be encouraged not to share needles because of the risk of HIV infection.

Approximately 28% of all mothers pass their HIV infection to their babies, and HIV can spread through breast milk during nursing. Anti-HIV medications taken by the mother may reduce the risk of spread to the child. Delivery by cesarean section can reduce the risk of HIV infection of the newborn to 1%.

Some modes of transmission are at greatly reduced risk of causing infection. HIV particles are found in saliva, but the risk of oral infection is so low that no case has ever been identified as being transmitted by kissing. Instances of HIV transmission from oral intercourse have been reported, however. HIV does not appear to be spread through sweat, tears, urine, or feces, or by indirect contact through towels, plates, or eating utensils.

Clinical Disease

The earliest symptoms of HIV infection include fever, headache, fatigue, malaise, and lymphadenopathy. These early flu-like symptoms disappear within 1 to 2 weeks, and represent the primary infection, characterized by massive amounts of HIV particles in the genital fluid. The patient is at extraordinary risk for spreading the virus during this phase.

A latent period of as long as a decade follows the initial infection characterized by a lack of symptoms. The virus is actively replicating during this period and infecting cells of the immune system, however. During this period a decline in the CD4 level occurs. As the immune system is slowly destroyed, enlargement of the lymph nodes occurs. An insidious onset of symptoms then occurs that includes fatigue, loss of weight, fever, sweats, skin rashes, and short-term memory loss. In addition, any patient with a sudden onset of herpes zoster dermatitis, particularly at a young age, should be evaluated for HIV infection.

Normal CD4 counts are 1000 cells per cubic millimeter of blood. The Center for Disease Control (CDC) has defined AIDS as occurring in HIV-infected patients with fewer than 200 CD4 cells/mm^3.

The CDC has identified 26 clinical conditions that may be present in cases of AIDS. These clinical entities do not usually affect healthy individuals, but can severely compromise the health of individuals with suppressed immune systems. These conditions include *Pneumocystis carinii* pneumonia, toxoplasmosis, cytomegalovirus, fungal infections, and Kaposi's sarcoma (Figure 14-1).

The time frame for untreated HIV infection follows a natural history that is fairly consistent among patients. From the moment of viral transmission, 2 to 3 weeks elapse until the patient experiences the onset

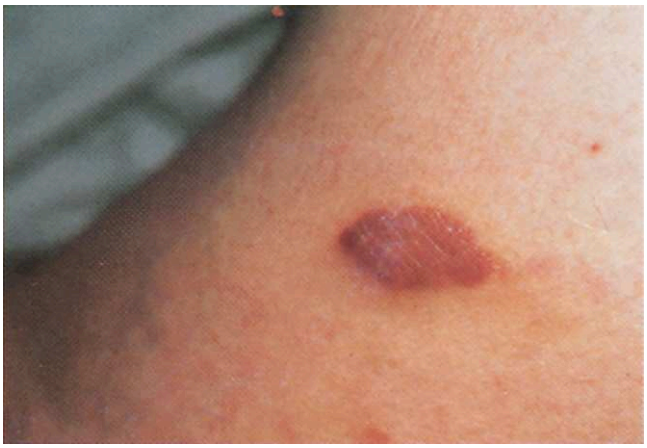

FIGURE 14-1 ■ Kaposi's sarcoma, a vascular malignancy common in AIDS patients. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 4, London, 2005, Churchill Livingstone.)

of acute retroviral syndrome (ARS). ARS is characterized by flu-like symptoms, including fever and lymphadenopathy, accompanied by precipitous decline in CD4 cell counts, high plasma viremia, and high concentrations of HIV RNA in the plasma. ARS lasts approximately 2 to 3 weeks until clinical recovery, defined as the period of time during which a reduction in plasma viremia occurs because of a cytotoxic T-cell (CTL) response. During this period, CD4 cell counts may remain low because of HIV-induced cell death. HIV RNA concentrations in the plasma begin to decrease because of the immune response. Recovery and seroconversion lasts yet another 2 to 3 weeks until the period of asymptomatic chronic HIV infection begins. This late stage of the disease lasts an average of 8 years and is characterized by a CD4 count between 600 and 200 cells/mm^3. When the CD4 count drops below 200 cells/mm^3, the stage of symptomatic HIV infection/AIDS begins and lasts an average of 3.7 years until death. This late stage of the disease is characterized by the development of opportunistic infections, tumors, neurologic complications, and wasting.

Complications

HIV complications can be correlated to CD4 counts. When the CD4 count drops below 500 cells/mm^3, as in the period of ARS, lymphadenopathy and myopathy may occur. When the CD4 count drops to between 200 and 500 cells/mm^3, pneumonia, tuberculosis, herpes zoster, Kaposi's sarcoma, cervical cancer, anemia, and Hodgkin's lymphoma may arise. Below 200 cells/mm^3, histoplasmosis, wasting, peripheral neuropathy, dementia, and cardiomyopathy occur. Most complications occur with increasing frequency at lower CD4 cell counts.

Laboratory Testing

Laboratory testing establishes the diagnosis of HIV infection by detecting antibodies to the virus or viral RNA/DNA, or by culture. Two serology tests exist for antibody detection, HIV-1 and HIV-2. Nearly all cases of HIV infection are HIV-1, and this type is divided into subtypes A, to O, and a more recently identified subtype, N. In the United States, 98% of all HIV-1 infections are caused by subtype B. HIV-2 is found predominantly in West Africa, is less transmissible, and is associated with a slower rate of CD4 cell decline and clinical progression. Standard serological testing for HIV infection includes an enzyme immunosorbent assay (EIA) screening test followed by a confirmatory Western blot (WB). Positive results should always be confirmed by repeat tests or corroboration of clinical or laboratory findings. False-positive HIV serology tests most often occur because of HIV vaccination. Alternative HIV serological tests include the IFA, in which HIV antibodies are detected by using patient serum reacted with HIV infected cells, home kits used to appropriate blood samples that are then sent to a laboratory, rapid tests, saliva tests for obtaining immunoglobulin G (IgG) and the detection of HIV antibodies, urine tests, vaginal tests (recommended for rape victims because HIV IgG antibodies are present in semen), and viral detection tests that establish HIV infection by detecting HIV antigen, DNA, or RNA.

Therapy

The goals of HIV/AIDS therapy are multifaceted, and include clinical, virologic, immunologic, and epidemiologic guidelines. Clinically, the prolongation of life and the improvement of the quality of life are of paramount importance. The medical goal seeks to obtain the greatest possible reduction in viral load for as long as possible to halt disease progression. The immunologic goal of HIV/AIDS therapy is the reconstitution of the immune system with restoration of a normal CD4 count. Finally, it is mandatory in any therapeutic regimen to address the epidemiologic goal of reducing HIV transmission.

Therapy for the patient with HIV/AIDS infection begins on the basis of the CD4 count, symptoms, and viral load. Treatment always commences when the CD4 count drops below 200 cells/mm^3. Studies have supported the concept that beginning therapy when the CD4 count is between 200 and 500 cells/mm^3 is of no or limited benefit. Viral load should theoretically predict progression of the disease independent of the CD4 count, and therefore should be taken into account when therapy is initiated. Studies have consistently shown, however, that the CD4 count at baseline is the single most important predictor of disease progression.

The mainstay of HIV/AIDS treatment is the antiretroviral drug, which was first formulated in 1987. The first drug was zidovudine, which was found to extend asymptomatic infection with CD4 counts below 500 cells/mm^3. Several years later, the combination of zidovudine with another reverse transcriptase nucleoside inhibitor was found to be of benefit in limiting disease progression. The development of resistance to these drugs was a common problem, however.

More recently, the introduction of protease inhibitors in combination with reverse transcriptase inhibitors, reduces HIV replication, sometimes to undetectable levels. As of this writing, seven nucleoside reverse transcriptase inhibitors (NRTIs) interrupt an early stage of the virus and prevent it from making copies of itself: three nonnucleoside reverse transcriptase inhibitors (NNRTIs), and four HIV protease inhibitors (PIs) interrupt the virus from making copies of itself at a later step in its life cycle.

The Food and Drug Administration (FDA) has introduced a third new class of drugs, known as fusion inhibitors, to treat HIV infection. Fuzeon (enfuvirtide, or T-20), the first approved fusion inhibitor, works by interfering with HIV-1's ability to enter into cells by blocking the merging of the virus with the cell membranes. This inhibition blocks the ability of the HIV virus to enter and infect the human immune cells. Fuzeon is designed for use in combination with other anti-HIV medications. Fuzeon reduces the serum viral load and may be active against HIV that has become resistant to current antiviral treatment modalities.

NRTIs act to prevent elongation of the viral DNA chain by blocking nucleosides, and also prevent replication by blocking reverse transcriptase from binding to essential sites. Examples of NRTIs include zidovudine or azidothymidine (Retrovir, or AZT), didanosine or dideoxyinosine (Videx, or ddl), xalcitabine or zalcitabine (Hivid, or ddC), and abacavir (Ziagen).

NNRTIs act only by preventing viral replication by blocking reverse transcriptase from binding to essential sites. Examples of NNRTIs include delavirdine (Rescriptor, or DLV) and nevirapine (Viramune, or NVP).

Protease inhibitors act on the binding to the catalytic site of the HIV enzyme aspartic protease and causes premature release of immature, noninfectious viral particles. Examples of PIs include saquinavir (Invirase, or SAQ), ritonavir (Norvir, or RTV), and nelfinavir (Viracept, or NLF).

These drugs are used in combination for highly reactive antiretroviral therapy (HAART). The concept of HAART was formulated in 1995. The initial combination of drugs best used for the new patient varies according to the source of the recommendation. The Department of Health and Human Services (DHHS) guidelines of February 2003, recommend starting treatment with a combination of one NRTI and one NNRTI. The initial regimen of the International AIDS Society-USA (IAS-USA) (based on *JAMA* 288:222, 2002) recommended two NRTIs with one PI, two NRTIs and one NNRTI, or three NRTIs.

As of February 2006, the DHHS guidelines for initial treatment of HIV/AIDS in adults advised the use of an NNRTI-based regimen that included efavirenz and (zidovudine or tenofovir) and (lamivudine or emtricitabine). An alternative to this treatment plan, also recommended by DHHS, is the use of efavirenz and (didanosine or abacavir or stavudine) and (lamivudine or emtricitabine).

Patient compliance was found to be the most significant factor influencing the success of therapy, with a strong correlation found between virologic response and adherence to therapy. Greater or equal to 95% adherence to HAART was necessary to achieve 80% viral suppression in an individual. Most failures within the first 6 months are caused by patient noncompliance with HAART, and late failures are caused by resistance to the drugs.

Failure of the HAART therapeutic regimen is reflected in an inadequate virologic response, which is caused by drug resistance, a lack of compliance to HAART, reduced potency of the regimen, and failure of the drug or drugs to get to the site of infection.

Treatment of Complications

Chronic HIV infection is characterized by secondary infections and tumor development that increase in frequency and intensity as the CD4 count decreases.

Pneumocystis carinii *Pneumonia*

One of the most significant complications of HIV infection is *Pneumocystis carinii* pneumonia, or PCP. Historically, the spread of PCP in American homosexuals with no known immune deficiency disease revealed the presence of HIV infection. A significant risk of PCP exists if the CD4 count drops below 200 cells/mm^3. PCP is seen clinically as a pulmonary disease characterized by dyspnea, dry cough, fever, and weight loss. Chest x-ray reveals bilateral, micronodular lesions. PCP may spread through the body to cause infection in the bone marrow, spleen, liver, skin, and retina. First-line agents to treat PCP include trimethoprim and sulfamethoxazole (cotrimoxazole), but other treatment regimens include pentamidine, trimethoprim, and sulfamethoxazole (TMP-SMX), dapsone with trimethoprim, and clindamycin with primaquine. Newer medications for the treatment of PCP include atovaquone and trimetrexate.

Cytomegalovirus Infection

The incidence of opportunistic infections in HIV-infected patients has fallen precipitously since the introduction of HAART, and improved outcomes exist

for viral infections, including cytomegalovirus (CMV). Before the widespread use of HAART, CMV infection was on the rise among HIV-infected individuals. The incidence of CMV in this population is now decreasing because of the effectiveness of HAART, but it remains the most common complication of HIV infection. CMV exists in approximately 60% of the U.S. human population, and 95% of homosexual males are infected with CMV.

Retinopathy is the single most common clinical manifestation of CMV infection or AIDS. Of all cases of CMV retinopathy, 85% occur in the environment of HIV infection or AIDS.

AIDS appears to cause reactivation of the latent virus. Patients in whom CD4 cell counts fall below 50 cells/mm^3 should have ophthalmoscopic evaluations every 3 to 6 months. Treatment of CMV retinopathy includes oral ganciclovir for primary prophylaxis of CMV retinitis in patients whose CD4 count falls below 100 cells/mm^3. HAART appears, in some studies, to reconstitute the immune system, thus returning CD4 levels back to higher levels, negating the need for anti-CMV therapy. Other studies suggest that HAART does not prevent reactivation of CMV virus, however, even in patients with elevated CD4 cell counts.

CMV infection causes a relentless and progressive unilateral retinitis that may eventually involve both eyes, if left untreated. Symptoms include blurred vision, floaters, and painless vision loss. On ophthalmoscopy, the retina reveals the presence of cotton-wool spots (Figure 14-2). These lesions appear as white, fluffy, perivascular exudates (Figure 14-3) and are accompanied by retinal hemorrhages (Figure 14-4).

CMV may also infect the gastrointestinal system, causing ulcers; the central nervous system, causing lower extremity pain; and the lungs, causing a dry, nonproductive cough.

Treatment of CMV infection in HIV/AIDS includes a nucleoside analog (ganciclovir), a pyrophosphate analog (foscarnet), and a nucleotide analog (cidofovir). Combination therapy of ganciclovir and foscarnet appears synergistic and is superior to either drug used alone. Intravitreal injection of an anti-CMV agent has been used to control CMV retinitis. Intravitreal implantation of devices containing ganciclovir has allowed for continuous dosing of the drug to the retina. Use of intravitreal devices or intravitreal injection of anti-CMV agent is associated with a higher incidence of contralateral CMV retinitis and systemic CMV infection, because a systemic anti-CMV agent is not being used.

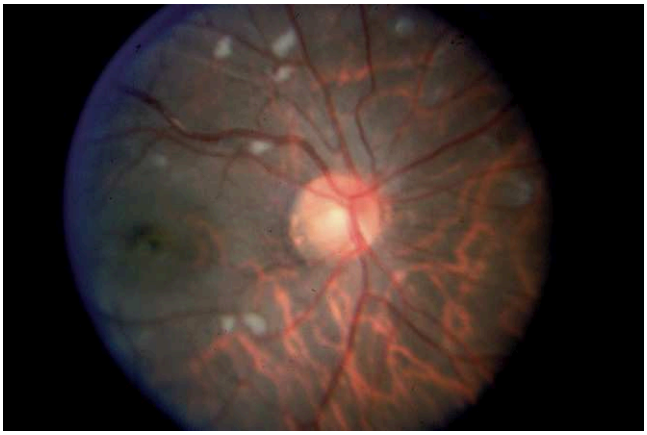

FIGURE 14-2 ■ Cotton-wool spots are the most common ocular manifestation of HIV infection.

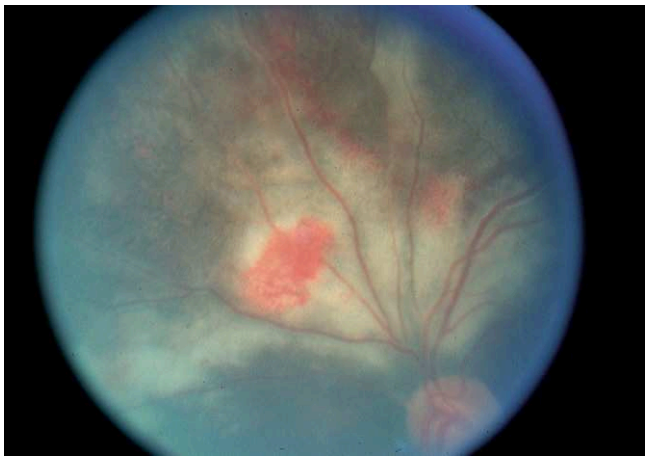

FIGURE 14-3 ■ Cytomegalovirus retinitis. Granular white patches along the retinal vessels and arcades.

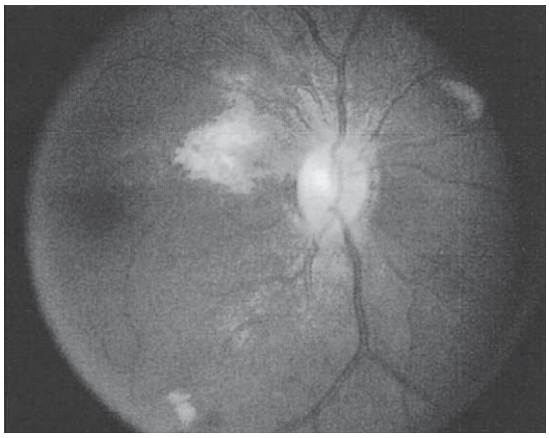

FIGURE 14-4 ■ Retinal hemorrhages, cotton-wool spots, microaneurysms, and ischemic macular edema in an HIV patient.

Herpes Zoster Virus Infection

Herpes zoster virus (HZV) infection may be the first indication of HIV disease. The patient exhibits a localized and segmental painful erythematous maculopapular rash along a single dermatome. The lesions evolve from vesicles to pustules during a 3-day period, erupting in painful episodes that are associated with bleeding lesions. Scabs eventually form over the

involved skin lesions. Within 1 month from initial outbreak, the scabs fall off revealing new, reddened skin formation. H. zoster of the trigeminal nerve may cause corneal scarring and permanent vision loss. H. zoster outbreak usually represents a reactivation of a virus obtained most commonly in childhood with an initial varicella-zoster virus, or chickenpox. The varicella virus that causes chickenpox migrates to the sensory nerve ganglia, where it becomes dormant. An HIV infection that causes a decrease in immune function causes the latent virus to become reactivated, causing a H. zoster outbreak.

Treatment of H. zoster in an HIV-infected individual requires specific antiviral therapy. Acyclovir reduces pain and shortens the duration of viral shedding, the duration of new lesion formation, the time to crusting of the lesions, and the time to complete healing. Localized H. zoster dermatitis is treated with 800 mg, 5 times daily, of oral acyclovir.

Herpes Simplex Virus Infection

Herpes simplex virus (HSV) infection may occur from HSV-1, acquired in childhood, or HSV-2, usually acquired through sexual contact. HSV has the capacity to establish latent infection in the dorsal root or sensory ganglia. Viral reactivation caused by the suppressed immune system of the HIV-infected individual can cause viral reactivation that leads to a painful, cutaneous, or mucosal lesion. Reactivation of HSV usually occurs in CD4 counts below 100 cells/mm^3. Recurrent HSV infections are managed with oral acyclovir, valacyclovir, and famciclovir therapy.

Tuberculosis

Active tuberculosis (TB) infection appears to accelerate the rate of HIV progression. HIV-positive individuals who are in close contact with active TB cases should be evaluated to exclude active disease and should receive prophylactic treatment for latent TB infection. Treatment for TB in an HIV-infected individual includes isoniazid (INH) and pyridoxine. Rifampin therapy has not been adequately studied in HIV-infected individuals.

Epidemiology of HIV/AIDS

The distribution and transmission patterns of HIV infection are staggering. In the 15 years since the first cases of AIDS in the United States were reported, 30 million people worldwide were estimated to have HIV infection and AIDS. In the same year six million people were estimated to have contracted HIV, with more than two million deaths occurring because of HIV infection and AIDS. Twenty years after the first cases were diagnosed, an estimated 40 million individuals were infected, 90% in developing nations. By that year, HIV was found in the populations of 190 countries and infection had reached pandemic proportions.

In the past quarter century, HIV/AIDS has evolved into a heterosexual disease on a worldwide basis. Subsaharan Africa has been particularly hard-hit, with the prevalence of adult HIV in some countries exceeding 30% in 1997, and now approaching 50%.

Varicella Zoster Virus and Herpes Zoster

Etiology

Infection by the varicella-zoster virus (VZV) causes varicella, or chickenpox, and herpes zoster, or "shingles." VZV is a Herpesviridae virus that consists of a lipid layer enveloping a nucleocapsid containing double-stranded DNA.

Infection

Initial infection by VZV usually occurs by inhalation of VZV particles. Replication of the virus then occurs, most often within the nasopharynx. The virus incubates for 10 to 21 days, and individuals are infectious 2 days before rash development. Spread of the virus occurs through the reticuloendothelial system. This body-wide seeding results in the diffuse skin lesions so classic of chickenpox. The vesicles involve the dermis and balloon outward as they fill with polymorphonuclear lymphocytes. Fever is typical during this time. Eventually, within a 1-week period, the vesicles rupture and release their highly infectious contents. Children aged 5 to 9 years are most susceptible to infection.

Resolution

During the primary infection, VZV infects the dorsal motor root ganglia. After resolution of chickenpox, the VZV remains latent until reactivation results in herpes zoster.

Reactivation

Reactivation of VZV does not appear to be caused by reinfection. It is most common in the elderly. The mechanism of reactivation is unknown, although stimuli such as trauma, stress, irradiation, and the presence of disease have been shown to be related to herpes zoster outbreak.

Herpes Zoster Prodrome

The onset of an H. zoster outbreak is often heralded by a 2- to 3-day prodrome of headache, fever, malaise, and chills. The patient may complain of a tingling sensation of the involved skin area. The skin becomes red, and vesicles break out over the dermis in a pattern consistent with the dermal distribution of a dermatome.

Herpes Zoster Appearance

The appearance of H. zoster is similar to chickenpox but is a unilateral vesicular rash that is confined to a single dermatome, most frequently T3 to L3 (Figure 14-5).

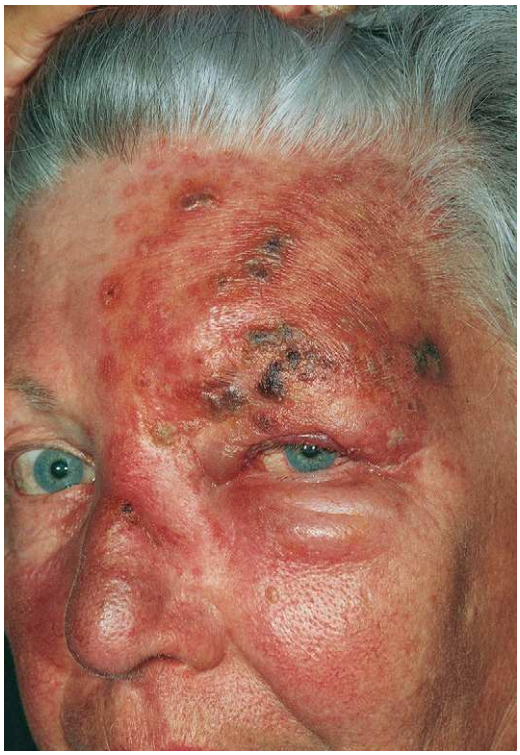

FIGURE 14-5 ■ Herpes zoster of the T7 and T8 nerve roots. Notice the clusters of small vesicles on a deeply erythematous background. Surrounding edema is usually present. (From Habif TB: *Clinical dermatology: a color guide to diagnosis and therapy,* ed 4, Philadelphia, 2004, Mosby.)

On reactivation, VZV migrates from the dorsal motor root ganglia, along the sensory nerve, and erupts at the dermatome or nerve ending. Vesicles may occur over the distribution of V1 to the forehead, V2 to the eye and cheek, or V3 to the chin. Combination of trigeminal branch involvement may also occur (Figure 14-6). The vesicles that compose the typical zoster skin rash fill with pus and erupt on the skin, causing bleeding and scab formation. This rash is a particularly painful involvement.

Herpes Zoster Ophthalmicus

Ocular involvement occurs in approximately half of all cases of H. zoster involvement. When the ophthalmic branch of the trigeminal nerve is involved, H. zoster ophthalmicus may result. If the nasociliary branch of the trigeminal becomes involved, then an eruption of the tip of the nose, known as Hutchinson's sign, increases the risk of corneal involvement. The presentation is nearly always unilateral and hemicranial. Ocular involvement causes conjunctivitis, anterior uveitis, or episcleritis. The formation of corneal ulcers is the most feared ocular complication. Hutchinson's sign should prompt repeated ocular evaluations after zoster dermatitis.

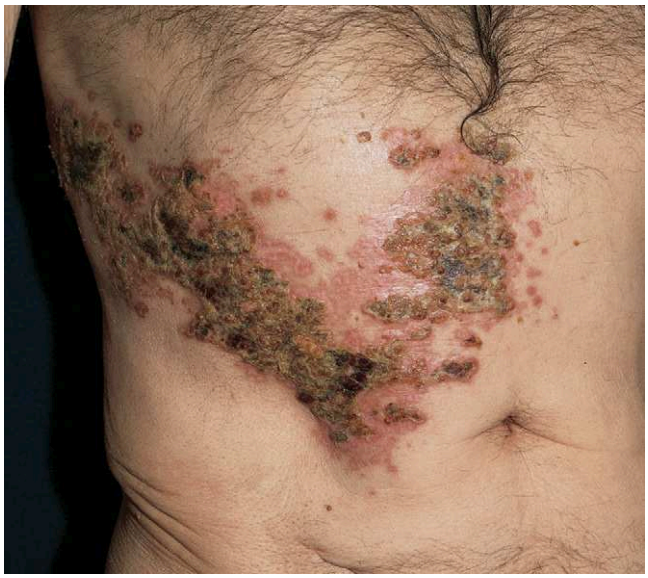

FIGURE 14-6 ■ Herpes zoster of the ophthalmic and maxillary fifth cranial nerve distribution. Eruption of blisters follows painful prodrome. (From Habif TB: *Clinical dermatology: a color guide to diagnosis and therapy,* ed 4, Philadelphia, 2004, Mosby.)

Herpes Zoster Keratitis

Corneal involvement begins within days of an outbreak and evolves from punctuate epithelial keratitis to pseudodendrite formation. Anterior stromal infiltrates may occur and may lead eventually to disciform keratitis months later (Figure 14-7). Disciform keratitis is highly amenable to the application of topical steroids.

Chickenpox Treatment

No treatment exists for chickenpox, and management strategies are directed toward good hygiene with daily baths and antipruritic drugs to reduce itching. For outbreak of chickenpox in adolescents and adults,

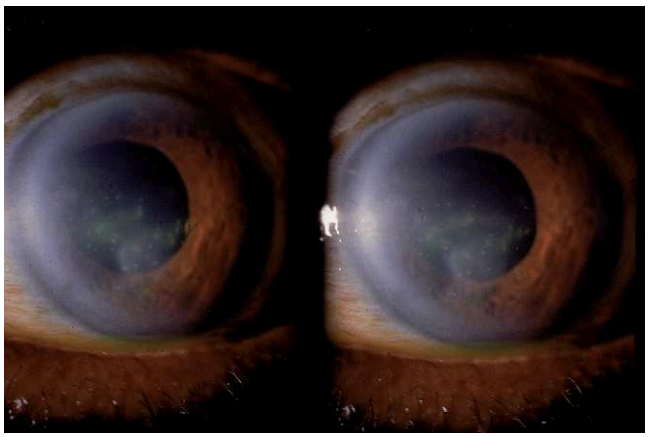

FIGURE 14-7 ■ Herpes zoster with corneal involvement. Note disk-shaped, discrete epithelial lesion of the cornea.

acyclovir therapy (800 mg, 5 times daily) is helpful and recommended.

Herpes Zoster Treatment

H. zoster outbreak mandates the use of oral antiviral therapy with acyclovir 800 mg, 5 times daily, as soon after the outbreak occurs as possible. If started within 72 hours of the outbreak, acyclovir may accelerate healing and reduce postherpetic neuralgia. Famciclovir (500 mg, 3 times daily, for 1 week po) may be used instead, or valacyclovir (1 g, 3 times daily, po, for 1 week). Herpes zoster in an HIV/AIDS patient must be treated with intravenous acyclovir.

Postherpetic Neuralgia

The most feared complication of H. zoster infection is an episodic, excruciatingly painful neuralgia known as postherpetic neuralgia (PHN) (Figure 14-8). Patients may become depressed, anxious, and even suicidal because of PHN. Management of these patients includes analgesics such as narcotics, oral prednisone, antianxiety medications, and psychological counseling.

Herpes Simplex

Etiology

Both forms of the herpes simplex virus (HSV-1 and HSV-2) contain double-stranded DNA and are closely related.

Infection

HSV enters through the mucosal linings of the mouth, nose, eyes, or labia by contact with cold sores or by sexual contact. Entry may also occur through abraded skin. HSV attaches to neuronal cell endings in the dermis. The virus is transmitted to the nerve cell bodies in the ganglia in which replication occurs.

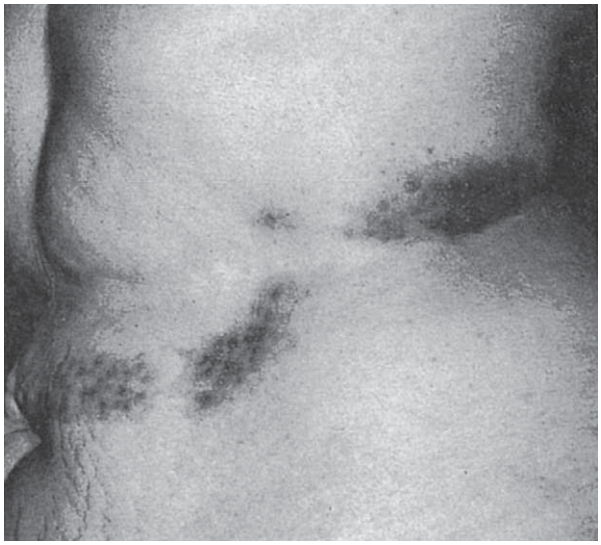

FIGURE 14-8 ■ Herpes zoster. Patchy distribution of lesion in the elderly may lead to postherpetic neuralgia for months or years. (From Habif TB: *Clinical dermatology: a color guide to diagnosis and therapy,* ed 2, St Louis, 1990, Mosby-Year Book.)

Replication

The HSV attaches to and fuses with the cell membrane. The nucleocapsid that contains the viral DNA is liberated into the cell cytoplasm, and the viral DNA is liberated and transcribed. Nucleocapsids containing replicated HSV DNA are assembled within the host cell. Viral particles are transported back to the cell membrane, where they exit the cell.

Reactivation

Some virus remains in intact neurons in a state of latency. For still unknown reasons, the H. simplex virus reactivates and then migrates out of the ganglia, spreading to mucosal (Figure 14-9) and skin surfaces (Figure 14-10) through peripheral sensory nerves (Figure 14-11). A number of factors have been postulated as stimuli for reactivation of latent H. simplex virus, but none have been confirmed. Triggers for virus reactivation may include physical or emotional stress, certain foods, ultraviolet radiation, steroid use, and trauma.

Pathophysiology

HSV-1 is transferred from patient-to-patient through contact with saliva or cold sores and causes the ocular manifestations of infection (Figure 14-12). HSV-2 is transferred by sexual contact and causes genital herpes infection (Figure 14-13).

Herpes Simplex Virus Prodrome

Reactivation of HSV-1 is heralded by a prodrome including ocular burning and stinging, paraorbital skin rash, conjunctival injection, photophobia, and blurry

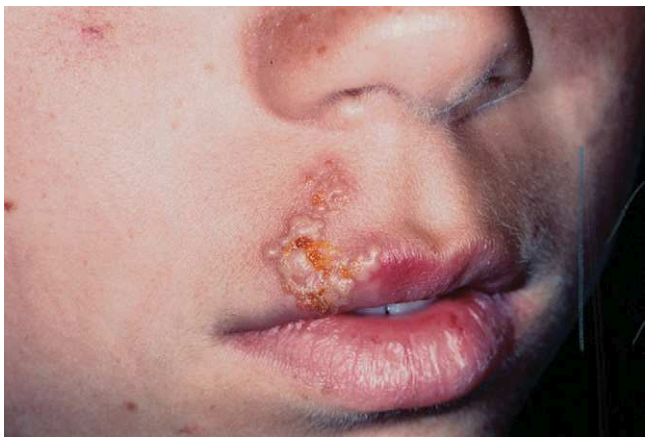

FIGURE 14-9 ■ Herpes simplex of the lips. There are clusters of small vesicles with surrounding pruritus and tenderness. These blisters rupture and leave serous crusts. (From Bolognia JL, Jorizzo JL, Rapini RP: *Dermatology,* St Louis, 2003, Mosby.)

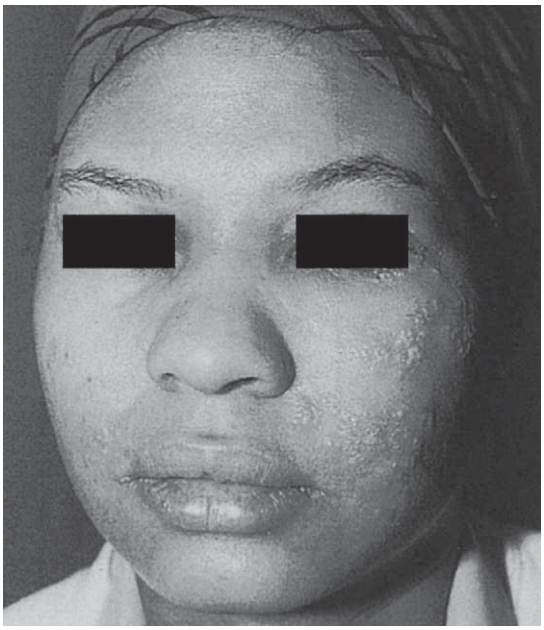

FIGURE 14-10 ■ Herpes simplex dermatitis. Note lesions on skin. (Courtesy Celeste Mruk, M.D.)

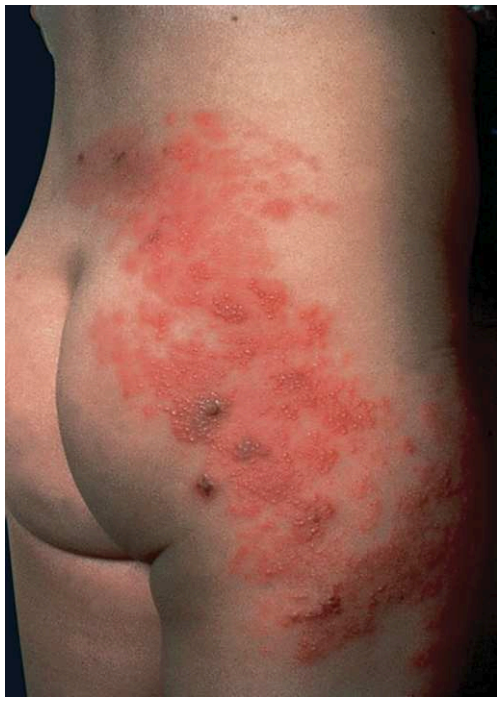

FIGURE 14-11 ■ Herpes simplex of the buttocks. The lesion consists of coalesced vesicles that have become pustular. (From Bolognia JL, Jorizzo JL, Rapini RP: *Dermatology,* St. Louis, 2003, Mosby.)

vision. The vast majority of ocular HSV infection is unilateral in presentation.

Ocular Herpes Simplex Virus Lid Infection

HSV can affect any and all structures of the eye. The lids may manifest dermatitis with characteristic clear vesicles on an erythematous base. These lid lesions may be confused with a zoster eruption (Figure 14-14). In all cases of vesicular eruptions of the eyelid, the cornea should be evaluated for dendritic ulcer (see below).

Herpes Simplex Virus Conjunctivitis

HSV may also cause conjunctivitis with tearing, epiphora, follicles, and pseudomembrane formation, all consistent with a viral infection.

Herpes Simplex Virus Epithelial Keratitis

HSV causes a classic dendritic ulceration of the corneal epithelium. The dendrite or dendrites resemble the branches of a tree (Figure 14-15), sometimes manifesting large terminal bulbs (Figure 14-16). The dendrite stains with both fluorescein and rose bengal. Obliteration of the branching appearance of the dendrite may occur because of stromal streaming of the fluorescein dye causing the dendrite to resemble a bacterial keratitis. Therefore, observation and documentation of the dendrite should occur immediately after installation of the fluorescein and before the dye migrates under the epithelium of the ulcers' edges. Rose Bengal stains the devitalized cells of the dendritic ulcer and can differentiate it from a corneal abrasion. Superficial punctuate keratitis (SPK) may be associated with the dendrite.

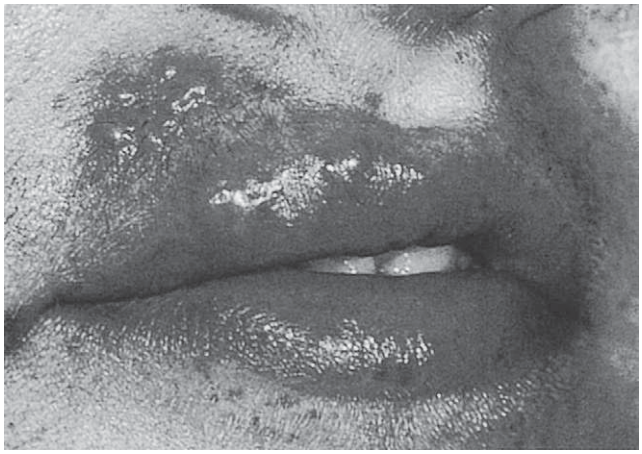

FIGURE 14-12 ■ Herpes simplex type I: Primary infection in children often includes gums with buccal ulceration and fever. Note skin lesions around lips. (From Habif TB: *Clinical dermatology: a color guide to diagnosis and therapy,* ed 2, St Louis, 1990, Mosby-Year Book.)

Epithelial HSV disease causes a relative corneal anesthesia that further helps to distinguish the lesion from an abrasion.

Herpes Simplex Virus Stromal Keratitis

Approximately 10% of dendritic keratitis patients develop corneal stromal involvement. A necrotizing interstitial keratitis associated with anterior uveitis may

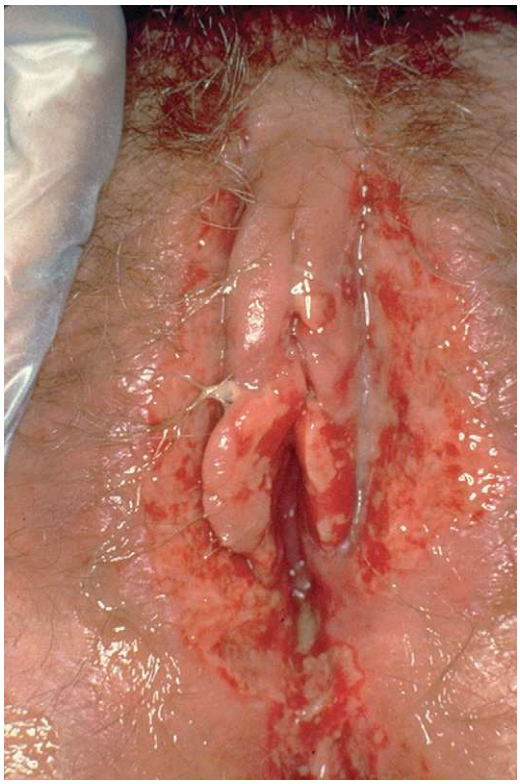

FIGURE 14-13 ■ Herpes simplex type 2: Genital herpes of the vulva demonstrates a superficial red, sharply marginated ulceration that is painful and recurrent. (From Mandell GL, Bennett JE, Dolin R: *Principles and practice of infectious diseases,* ed 6, Edinburgh, 2005, Churchill Livingstone.)

precipitate corneal neovascularization and thinning. Repeated bouts of stromal inflammation may result in perforation or a disciform scar.

Herpes Simplex Virus and Other Ocular Findings

HSV can cause glaucoma because of a trabeculitis with permanent scarring of the meshwork. An anterior chamber reaction with cells and, rarely, small keratic precipitates (KPs), indicates a nongranulomatous iritis that often accompanies dendritic ulcer. HSV can cause vasculitis, retinal hemorrhaging, and areas of retinal necrosis.

Herpes Simplex Virus Autoinoculation

Autoinoculation of HSV is possible in a patient who engages in picking of a nostril cold sore and then proceeds to immediately scratch the skin. This may result in an outbreak of vesicles occurring in a straight line, particularly around the eye. This outbreak is not the result of involvement of a dermatome, as seen in zoster infection.

Systemic Treatment

HSV dermatitis is self-limiting, and antiviral medication does not appear to promote resolution or healing of the skin involvement. Appropriate skin hygiene can help

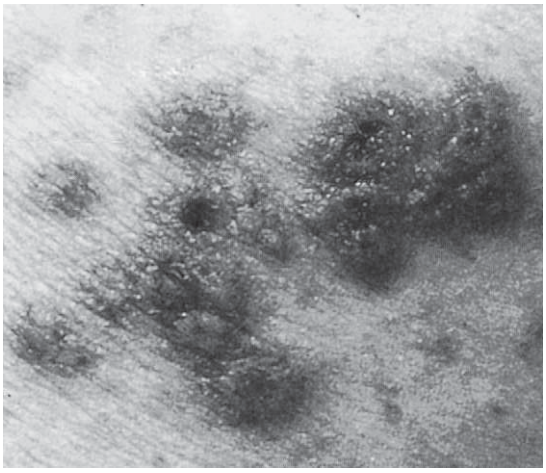

FIGURE 14-14 ■ Herpes simplex may resemble herpes zoster, as in this unilateral presentation of herpes simplex on the cheek. (From Habif TB: *Clinical dermatology: a color guide to diagnosis and therapy,* ed 2, St Louis, 1990, Mosby-Year Book.)

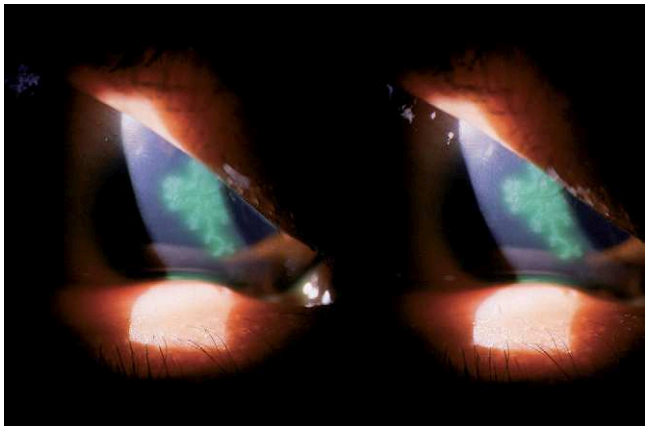

FIGURE 14-15 ■ Herpes simplex virus causing an epithelial infectious ulceration known as dendritic keratitis. Note "Christmas tree" appearance of stained lesion.

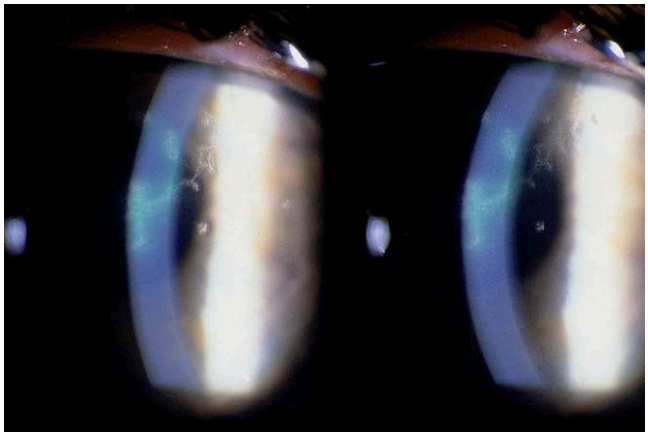

FIGURE 14-16 ■ Herpes simplex of the cornea.

reduce the risk of secondary bacterial infection. Healing of skin lesions occurs within 2 weeks without scarring.

Topical Treatment

Vesicular eruptions along the eyelid margin are treated with vidarabine, 3% ophthalmic ointment, 4 times daily for 1 week. Trifluridine 1% ophthalmic solution, may be used 4 times daily for HSV conjunctivitis to reduce the risk of keratitis. Dendritic ulcer is best treated with trifluridine, 1%, every 2 hours, not to exceed 9 times daily. This treatment is used for 7 to 10 days. After reepithelialization of the cornea, the trifluridine is used 4 times daily for 5 additional days. Total treatment should not exceed 21 days because of the risk of corneal toxicity. Long-term treatment of HSV dendritic ulcer involves the use of oral acyclovir, 400 mg, by mouth, twice daily for 1 to 2 years. This regimen reduces the risk of recurrent HSV disease.

Human Papillomavirus

Etiology

Human papillomaviruses (HPVs) are DNA viruses that infect the epithelium and mucous membranes. These nonenveloped viruses contain double-stranded DNA. More than 80 papilloma types exist, distinguished by their nucleic-acid sequences. Each type produces a specific and unique clinical entity, ranging from common skin warts to benign or malignant tumors. HPV incubates from 1 month to 2 years in the basal cells. Replication results in hyperkeratosis of the skin.

Warts

Caused by the verruca vulgaris HPV, these common skin manifestations infect a quarter of the world's population and are found most commonly in children. This common wart is elevated, multilobulated tissue attached by a stalk to the underlying skin. Treatment of verruca includes excision, laser ablation, or the use of dichloroacetic acid (bichloracetic acid).

Anogenital warts are caused by *Condyloma acuminatum* and are the most common of all sexually transmitted diseases (STDs). Squamous cell carcinoma of the cervix can be caused by HPV infection of the uterine cervix. Most warts are flesh-colored and appear on the hands, face, neck, arms, and legs.

HPV vaccination trials have begun and show some promise in the prevention of infection.

Smallpox (Variola)

Etiology

The variola virus is one of nine pox viruses that can infect humans. This DNA virus can cause ocular complications. Although smallpox was declared eradicated in 1980, the virus has reemerged as a possible bioterrorism agent.

Infection

Transmission of smallpox occurs through inhalation of infectious particles, or by skin-to-skin contact. After exposure to the smallpox virus, infection of the mucous membranes of the nose, mouth, and throat occurs and is accompanied by a high fever, headache, and fatigue. Within 2 days, the virus spreads into the skin and causes characteristic lesions on the face, forearms and, eventually, the legs. The smallpox skin involvement evolves from a maculopapular rash to pus-filled vesicles. In cases of hemorrhagic smallpox, bleeding may occur from all orifices. In the eyes, symblepharon may result from scarring of the erupting vesicles. Corneal infiltrates may lead to ulceration, perforation, and panophthalmitis. Corneal scarring results in permanent vision loss.

Treatment

No treatment exists for smallpox. Postexposure vaccination delivered within 3 days after infection may avert the disease. All patients suspected of having smallpox must be isolated. The last case of smallpox was reported in 1977 in Somalia, although samples are in existence that may prove to be an effective bioterrorism agent. Most of the smallpox virus has been destroyed, and the remaining two repositories in the world are in Russia and at the Center for Disease Control in Atlanta.

Measles (Rubeola)

Etiology

The highly contagious rubeola virus contains RNA and belongs to the myxovirus group. It is usually acquired in childhood and is transmitted by direct contact.

Childhood Infection

Acute rubeola causes a mild fever with a bodywide rash, which may be associated with conjunctival injection, tearing, and photophobia. All children who contract measles must be followed closely for encephalitis, which occurs within a week of the onset of the rash. Encephalitis causes fever, drowsiness, headache, and vomiting. Visual loss is dramatic, and ophthalmoscopy reveals optic disc and macular edema with venous dilation. Optic atrophy can result from rubeola encephalitis.

Complications

Intensive exposure to measles in children younger than 2 years old is associated with a devastating retinal condition known as subacute sclerosing panencephalitis, or SSPE. This condition causes cerebral signs (i.e., forgetfulness), convulsions, and coma. SSPE occurs most often in boys between the ages of 5 and 15 years old

who live in rural farm communities. Death occurs within a year of onset. Half of the patients with SSPE have ocular symptoms or signs, including visual hallucinations, blindness, ocular motility dysfunction, and fundus changes. Retinal characteristics of SSPE include papilledema, optic neuritis, optic atrophy, and retinitis. Measles vaccination has caused a precipitous drop in cases of SSPE.

Ocular Signs

In addition to conjunctivitis, macular edema, and disc edema, a measles retinopathy may occur. These retinal changes resemble retinitis pigmentosa, with bony spicule formation, optic atrophy, and attenuated blood vessels. No treatment exists for measles retinopathy.

Congenital Infection

Rubeola infection in a woman in the first trimester of pregnancy can cause fetal changes that result in cardiopathy, cataracts, and retinopathy in the newborn. Congenital rubeola results in a salt-and-pepper fundus, but vision usually remains good.

Rubella (German Measles)

Infection

Rubella, or German measles, has been largely eradicated by intensive vaccination programs. Nonetheless, at least 20% of women of childbearing age in the United States are susceptible to rubella, and contraction of the virus in the first trimester can be devastating to the fetus. The virus crosses the placental barrier and infects the fetus. Infection of the fetus during the first trimester results in congenital rubella 80% of the time. The stigmata of congenital rubella may not develop for years after birth.

Complications

The most common complication of rubella is hearing loss, but this remains difficult to diagnose. Of children with congenital rubella, two thirds develop heart disease. Other systemic manifestations include mental retardation, endocrinopathies, and vascular abnormalities.

Ocular Findings

Fully half of all children with congenital rubella develop ocular manifestations. The most common anterior complication is cataracts, although corneal edema, glaucoma, microphthalmos, nystagmus, high refractive error, and strabismus may also occur. Posterior segment involvement causes the development of rubella retinopathy. This condition consists of a salt-and-pepper fundus pigmentary change that results in a mottled, irregular retinal pigmentation of the macula. The foveal reflex is absent in cases of rubella retinopathy. In addition, peripheral retinal changes results in a dusting of pigment. The optic nerve may become pale, but visual acuity remains normal. This retinopathy requires no treatment.

Treatment

Immunization has almost eliminated congenital rubella in the United States, but it is still possible because one fifth of all women of childbearing age are susceptible to infection.

No therapy exists for rubella, and treatment is aimed at controlling the fever, arthralgia, and arthritis associated with the viral infection.

Mumps

Etiology

Mumps is an RNA myxovirus transmitted by the airborne route from the saliva of an infected individual and inhaled by the new host. In the spring of 2006, a fascinating outbreak of mumps occurred throughout the northern Midwest portion of the United States. Although the factors involved in the dramatic outbreak still have not been fully qualified, it was discovered that several cases spread quickly because of airline travel. These cases demonstrate the impact of modern travel on the spread of virulent infections.

Systemic Manifestations

Patients experience a 2-week course of fever, malaise, and lymphadenopathy. Most often the patients' lymph nodes swell, causing pain with movement.

Ocular Manifestations

The anterior segment manifestations of mumps include follicular conjunctivitis, keratitis, iritis, episcleritis, glaucoma, and lacrimal gland enlargement. Posterior segment manifestations of mumps include optic neuritis and choroiditis.

Congenital Infection

Maternal infection of mumps during pregnancy results in fetal damage, including congenital cataracts, nystagmus, optic atrophy, and retinal abnormalities.

Treatment

In 1995 less than a thousand cases of mumps were reported in the United States because of effective immunization programs.

Epstein-Barr Virus

Etiology

Epstein-Barr virus (EBV) is ubiquitous, and most adults are infected with it.

Infection

Primary infection of EBV causes host production of IgG and IgM antibodies that attack the virus capsids. IgG levels remain elevated for the rest of the patients' life, and IgM drops to near undetectable levels. B lymphocytes are infected by EBV antigens. L lymphocytes target these infected B lymphocytes, decreasing the level of EBV antigens throughout the patients' lifetime.

Systemic Manifestation

The virus manifests as mononucleosis, which causes extreme fatigue and lethargy for as long as 6 weeks.

Ocular Manifestations

EBV is associated with chorioretinitis. Cases of ocular EBV are characterized by multifocal choroiditis and mild panuveitis. The retina displays multiple, small chorioretinal scars, peripheral pigmentary changes, and macular choroidal neovascularization caused by infection of the retinal pigmentary epithelium (RPE). The ocular manifestations of EBV typically occur in young adults, whose symptoms range from blurry vision to metamorphopsia, floaters, scotomata, and photopsias. Vision may be reduced to light perception. Therefore, all patients with known EBV should be evaluated with a dilated fundus examination.

Treatment

The treatment of EBV includes the use of an antiviral agent, such as acyclovir, with a steroid agent. Choroidal neovascularization is treated with laser therapy.

BACTERIAL INFECTIONS

Gram-Positive Infections

Streptococcus

Alpha- and beta-hemolytic streptococci, and *Streptococcus pneumoniae*, are the two types of *Streptococcus* bacteria with significant ocular ramifications. *Streptococcus* bacteria are spheroidal in shape and exist in long chains. *Streptococcus* test positive on Gram's staining, hence its classification as a gram-positive bacteria. These bacteria are part of the normal human flora and are found primarily in the lungs, gastrointestinal (GI) tract, and genitourinary tract.

Streptococcus bacteria infect and multiply within tissues and release enzymes that result in pathology. Systemic infection can cause pharyngitis with a concomitant sore throat, rheumatic fever, kidney infection, and meningitis.

Ocular infection by streptococci typically induces a blepharitis, although deep involvement can produce preseptal or orbital cellulitis. Preseptal cellulitis is an inflammatory condition of the lids that produces swollen and taught skin. The upper lid fold is obliterated, and the lid swelling is painful to the touch. This condition may be caused by infection, insect bite, trauma, or hordeolum. It is treated effectively with cephalexin (Keflex), and usually begins to subside within 3 days.

Orbital cellulitis is a much graver situation, because the eye may become proptotic and the patient may notice diplopia. Pain may be present on extraocular muscle excursions, and a limited motility may be noticed on the involved side. The patient may experience reduced vision on the involved side if the optic nerve becomes involved. Any patient seen with diplopia, pain on eye movement, proptosis, and reduced vision, should be referred to an emergency room and receive immediate orbital imaging.

Streptococcus is sensitive to erythromycin and penicillin.

Staphylococcus

Like *Streptococcus, Staphylococcus* bacteria are spheroids. These bacteria exist in clusters, however. They stain positive in Gram testing.

Staphylococcus bacteria cause pathology through the release of exotoxins and enzymes. *Staphylococcus* bacteria infect the skin and mucous membranes and can cause toxic shock syndrome, urinary tract infections (UTIs), skin infections, bacteremia, surgical wound infections, and food poisoning. The most important genus is *Staphylococcus aureus*. *Staphylococcus* bacteria infect through a break in the skin, and the colony releases enzymes that aid replication. These organisms are sensitive to bacitracin, gentamicin, the cephalosporins, and erythromycin.

Two forms of staphylococci most commonly infect the eye: *S. aureus* and *Staphylococcus epidermis*. The most common cause of blepharitis is infection by staphylococci. In addition, a suppurative exudate of the conjunctiva may occur. The treatment of *Staphylococcus* blepharitis and conjunctivitis makes use of warm compresses and lid scrubs. Antibiotic agents effective in the treatment of *Staphylococcus* blepharitis and conjunctivitis include ofloxacin drops, 4 times daily, and Polysporin ointment at night. The treatment regimen should be continued for 2 weeks.

Diphtheria

Caused by a gram-positive rod, *Corynebacterium diphtheriae*, this infection of the skin or mucous membranes causes pseudomembrane formation at the site of infection. Spread by close personal contact and incubating for less than a week, this disease can cause skin lesions and respiratory symptoms. Because of immunization programs, less than 5 cases of diphtheria occur per year in the United States.

Diphtheria produces a toxin that results in the respiratory tract infection. A significant complication is a

cardiac toxicity that occurs in up to a quarter of all infected individuals. The EKG pattern demonstrates changes and myocarditis may result. Neurologic toxicity is rare.

The treatment of diphtheria involves the intravenous administration of diphtheria antitoxin, which is produced from horses. Allergic response is possible in patients with equine allergy.

Tetanus

Clostridium tetani is a gram-positive rod found in the soil. The bacteria release a powerful protein toxin called tetanospasmin that causes a neurological disorder in humans.

Tetanus most often spreads by wound contamination with bacterial spores in cases of acute injury from a puncture wound or burns. Infection usually occurs in devitalized tissues. Release of the toxin is followed by entry of tetanospasmin into the nerve axon and its transport into the brain or spinal cord. The toxin causes spasms and increased muscle tone approximately 1 week after injury. Increased tone of the jaw muscle is followed by pain in the neck, shoulder, and back.

Treatment occurs in an intensive care unit (ICU) and consists of an antibiotic (penicillin or metronidazole) and an antitoxin (human tetanus immune globulin-T16). Diazepam may be administered to control spasmic activity.

Prevention of tetanus is possible with a series of vaccination injections followed by a booster every 10 years.

Botulism

Botulism is a clinical syndrome induced by any of the seven neurotoxins produced by *Clostridium botulinum* and related species of bacillus. *Clostridium botulinum* is a gram-positive organism found in soil and marine environments. The protein neurotoxin is the most powerful known in the world.

The bacteria may spread by food poisoning or wound contamination. Infection may also occur by inhalation of the bacillus. The incubation period is 18 to 36 hours, and within a day or 2 the symptoms of botulinum intoxication occur and are manifested by dry mouth, constipation, and urinary retention. The neurotoxin produces a descending paralysis and the onset of symptoms begins, with cranial nerve involvement causing diplopia and dysphagia, weakness, nausea, vomiting, dizziness, and blurred vision. Eventually death occurs because of respiratory failure. If treated appropriately and quickly, recovery is possible, however, but may take months. Antitoxin exists but must be given before exposure to the bacteria. If given after exposure, respiratory failure is still possible. Equine-derived antitoxin is useful for food-borne botulism poisoning.

The ocular effects of botulinum intoxication include dilated and fixed pupils with diplopia in an otherwise healthy patient. An outbreak of similar conditions may point to terrorist involvement using botulism neurotoxin as an aerosolized biological weapon. Other ocular findings include ptosis, extraocular muscle palsy, swallowing difficulties, and skeletal muscle weakness.

Botulinum toxin is used in the treatment of strabismus and blepharospasm.

Gram-Negative Infections

Gonorrhea

Neisseria gonorrhoeae is an STD that causes cervicitis, urethritis, proctitis, and conjunctivitis (Figure 14-17). In the United States, 315,000 new cases occur annually. It produces an acute urethritis 2 to 7 days after exposure, with a mucopurulent or purulent urethral discharge. Systemic treatment uses third-generation cephalosporins, such as ceftriaxone, with fluoroquinolones for antichlamydial activity. A vigilant search for concurrent *Chlamydia* infection should be undertaken.

The ocular manifestations of this STD include a hyperacute bacterial conjunctivitis with onset of symptoms within 12 hours of ocular exposure to the pathogen. The involved eye becomes red, irritated, and produces a purulent discharge. The eyelids are typically stuck together on awakening. Slit-lamp evaluation reveals a severely injected conjunctiva. Copious purulent discharge is present, with pseudomembrane formation in the cul de sac. The preauricular lymph nodes may be tender and enlarged and the cornea may exhibit superficial punctuate keratitis (SPK) or ulceration. Iritis and dacryoadenitis may also occur. Topical treatment includes the fluoroquinolones. *N. gonorrhoeae* may spread to the bloodstream through the conjunctiva and can result in septicemia.

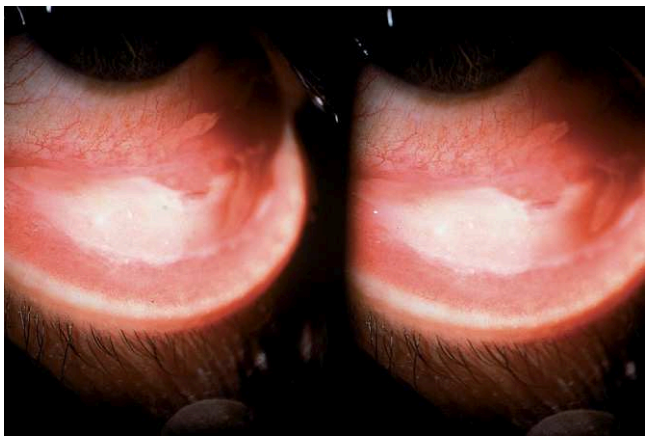

FIGURE 14-17 ■ Gonococcal conjunctivitis, a rapidly progressive, purulent conjunctivitis.

Condoms are effective in the prevention of transmission of gonorrhoeae.

Moraxella

These gram-negative cocci infect the respiratory tract and are a leading cause of otitis media and sinusitis. *Moraxella* is also a cause of chronic bronchitis. Most infected individuals are older than 50 years of age and have chronic obstructive pulmonary disease (COPD). Treatment involves penicillin or the cephalosporins. *Moraxella lacunata* may cause conjunctivitis.

Haemophilus

Spread by airborne droplets or by direct contact, these gram-negative organisms infect the upper respiratory system, and may spread to the meninges, bones, and joints. Clinical manifestations include meningitis, epiglottitis, and cellulites of the head or neck. *Haemophilus* is a leading cause of pneumonia. Two species of *Haemophilus* bacteria impact on ocular disease: *Haemophilus influenzae* and *Haemophilus aegyptius.* These gram-negative bacilli are pleomorphic and can cause blepharitis and cellulites. These bacilli are sensitive to penicillin, polymyxin B, and erythromycin. The meningitis is treated with cephalosporins and corticosteroids.

Legionella

Known as Legionnaire's disease, pneumonia caused by *Legionella* is spread by inhalation of the organisms. Patients experience diarrhea and fever. The pathology is usually confined to the lung, but it may also affect the heart, lymph nodes, and pancreas. Legionnaire's disease is treated with azithromycin and the quinolones (such as ciprofloxacin).

Escherichia coli

Escherichia coli is a gram-negative bacilli of the enterobacteria family. It causes less than 2% of all blepharitis. Gentamicin, ampicillin, polymyxin, and tobramycin are all effective against *E. coli.*

Pseudomonas

Pseudomonas aeruginosa is the most common human pathogen in this group of gram-negative bacteria. Found in soil, water, plants, and animals, *P. aeruginosa* has a single flagellum it uses for movement. This organism produces significant enzymes and exotoxins to break down host tissues and promote infection. It can cause pneumonia, bacteremia, endocarditis, meningitis, ear and bone infection, and urinary tract infections (UTIs). Systemic treatment of *Pseudomonas* infection includes penicillin (piperacillin), cephalosporins, or aminoglycosides (tobramycin).

P. aeruginosa is a cause of corneal bacterial ulceration. The bacteria gain entry into the eye through an epithelial break resulting from a corneal injury. Once the organism enters the corneal stroma, infection results in bacterial keratitis. Extended-wear contact lenses can increase the risk of infection. The keratitis starts as a small central ulcer and spreads outwards in concentric rings. Corneal perforation may ultimately result. A concurrent anterior chamber reaction is usually present. Treatment for the keratitis includes tobramycin eye drops or topical ciprofloxacin or ofloxacin.

Tuberculosis

The chronic, infectious disease tuberculosis (TB) is caused by the acid-fast bacterium *Mycobacterium tuberculosis.* Infection most often occurs by inhalation of bacterial particles, and thus the disease most commonly affects the lungs. Dissemination of the bacillus throughout the body may cause any organ or tissue to become involved (Figure 14-18).

After the infected air droplets are inhaled, the bacteria induces low-grade respiratory signs and symptoms, including a cough, fever, lymphadenopathy, and muscle aches. This primary infection may be overlooked by the patient and lasts only a week or two. During this initial phase of the disease, the host mounts an immunological defense against the bacillus. This results in elimination of the vast majority of the tuberculosis bacilli.

The remaining bacteria, being the most resistant to the immune response, survive the initial assault and encapsulate themselves within a protein envelope. In this way the surviving bacteria become invisible to the immune system. The tuberculin bacilli will then lay dormant within the host's tissues for the life of the patient. Meanwhile, the initial exposure to TB has

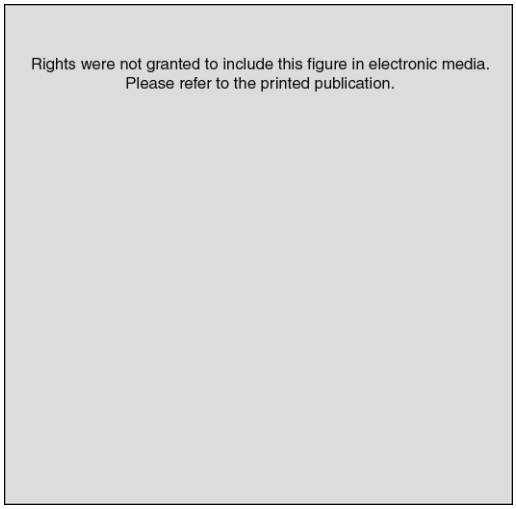

FIGURE 14-18 ■ Extrapulmonary manifestation of tuberculosis. (From Lawrence CM, Cox NH: *Physical signs in dermatology: color atlas and text,* London, 1993, Wolfe Medical Publishers, Ltd.)

sensitized the immune system and primed its components to respond to a second exposure.

A second exposure to *M. tuberculosis* bacilli can be devastating to the patient. Because of the previous exposure the immune system mounts a response so overwhelming that host tissues can be destroyed. In addition, a second exposure to TB stimulates the latent bacilli to lose their capsules. The sudden and dramatic presentation of these bacterial antigens further heightens the immune response, causing even more tissue destruction.

Pulmonary cavitation and hemorrhaging may occur. The patient experiences prolonged and productive coughing, sometimes with hemoptysis. Fever, chills, night sweats, body aches, weight loss, malaise, and lymphadenopathy may accompany the cough. Because all body tissues may be involved, signs and symptoms may vary.

TB generates a granulomatous response in body tissues. Nodular formation within the lungs occurs, and these tubercles induce tissue necrosis (Figure 14-19). If the granulomatous tubercle occurs in the lung apex, a Horner's syndrome with ipsilateral ptosis and miosis may occur. This is to the result of disruption of the sympathetic nerves coursing from the spinal cord to synapse in the superior cervical ganglion within the neck.

In the eye, TB is a rare cause of anterior uveitis. More often the infection involves the posterior segment, with clinical signs including vitreous floaters, choroidal lesions, vitritis, papillitis, and ocular granulomas that can occur in any ocular tissue.

Laboratory testing for tuberculosis infection includes a purified protein derivative (PPD) test and anergy panel. In addition, chest x-ray, erythrocyte sedimentation rate (ESR) and sputum culture are of value.

The treatment of TB is usually coordinated with a pulmonologist and includes multiple drug therapy. Isoniazid (INH), ethambutol, and rifampin are traditionally used in various amounts and combinations during a 9- to 12-month period. Streptomycin and ethambutol may also be used in combination with the other medications depending on individual protocol. Vitamin B_6 supplementation is prescribed to prevent nutritional deficiency, and corticosteroids may reduce inflammation in highly involved cases.

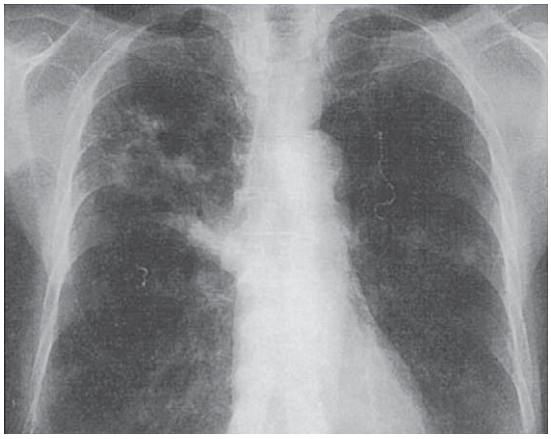

FIGURE 14-19 ■ Tuberculosis. Chest radiograph demonstrates cavitary destruction of upper lung fields. (Courtesy Celeste Mruk, MD.)

In the United States 30,000 new cases of TB are diagnosed each year, and more than a billion people worldwide have been infected. A recent rise in TB cases has occurred because of the large number of HIV/AIDS individuals who act as a reservoir for the bacilli.

Spirochetal Infections

Lyme Disease

This infection is caused by the bacteria *Borrelia burgdorferi.* It is spread by the bite of a tick, most commonly the *Ixodes scapularis*, or deer tick. However, it is important to note that all species of ticks in the United States have now been shown to be capable of transmitting the spirochete. The deer tick is the most significant reservoir for Lyme disease bacteria. These are small ticks, more than half the size of the much larger and more commonly seen wood tick. In general, ticks are less infectious in the springtime. In the summer and fall, the population of Lyme bacteria increase, and consequently tick bites that occur in autumn carry a higher risk of Lyme disease transmission. The nymph stage of the tick is most responsible for Lyme disease in humans. The larger adult ticks have less risk of spreading the disease.

Since its discovery in a population of patients in 1980 in Lyme, Connecticut, Lyme disease has spread through the human population around the world. In addition, the bacteria have been found in vast numbers of other animal species, including birds, lizards, amphibians, and other mammals.

Infection in all cases of Lyme disease is by the tick, and the ticks have been disseminated worldwide through the avian vector. Ticks often climb onto the backs of birds where they will engage in a blood feast. The birds may migrate hundreds or thousands of miles and transport insects great distances. This aviancentric transportation mechanism was first deduced decades ago, when patterns of Lyme disease infection were found to mirror bird migration routes. Lyme disease spread from Connecticut to Florida along the same Atlantic flyway that many eastern bird species follow. More slowly, Lyme disease spread along the northern tier of states from Maine to Oregon because a single species, the European Starling, migrates in an east-west direction. A bird species introduced into the United States

a century ago, the starling follows its ancestral African migration.

Ticks acquire the spirochetal bacteria from two primary animal reservoirs in the United States: the white-tailed deer (for adult ticks), and the white-footed mouse (for the nymph stage). Other animals can act as reservoirs for the bacteria, however, and this helps the disease spread worldwide. Curiously, although diverse animal species are infected by the bacteria, many do not seem to manifest the symptoms of Lyme disease. White-tailed deer, for example, seem completely unaffected by the infection. It is in the human and the dog that the profound and debilitating effects of Lyme disease are most profound and most readily apparent.

Ticks are most common in forests and tall grass. It is the habit of ticks to climb blades of grass and await contact with an animal, at which point the tick climbs to an isolated area on the body, preferably where there is hair or fur. Ticks have been known to drop from trees onto animals without any physical stimulation, most likely sensing the warmth or moisture that the passing animal emits. Ticks are found year-round, even in cold, snowy regions, and survive by finding safe harbor within the fur of mammals. In this way, human tick bites can occur even in the winter in northern climates.

Once the tick lights on a suitable host, it climbs a hair follicle and uses its mouth parts to immerse its head into the dermis. The tick releases a local anesthetic during its slow and deliberate bite so that the host does not feel any pain.

While the tick engages in a blood feast, a slow transmission of the bacteria into the host's bloodstream occurs. Transmission of the bacteria is thought to require a bite of at least 24 hours duration. Therefore, a recently imbedded tick, that is, one that is not swollen with blood and is easily removed, poses little risk of transmission.

A tick that is swollen with blood and removed with great difficulty carries an increased risk of transmission.

Once the bacteria have been transmitted, they replicate within the dermis. The spirochete spreads fairly rapidly in the skin and then disseminates throughout the body. This process causes a nonspecific immune response, including macrophages, monocytes, B cells, and compliment. The area on the skin where the bite took place may reveal a dime or quarter-sized pinkish-red, flat rash. This is not the classic rash of Lyme disease, but a local reaction because of the bite and the secretory juices of the tick.

The Lyme disease rash, which may take days or weeks to appear, is silver dollar-sized, and is seen in only one third of cases of infection (Figure 14-20). The Lyme disease rash may occur away from the site of the bite.

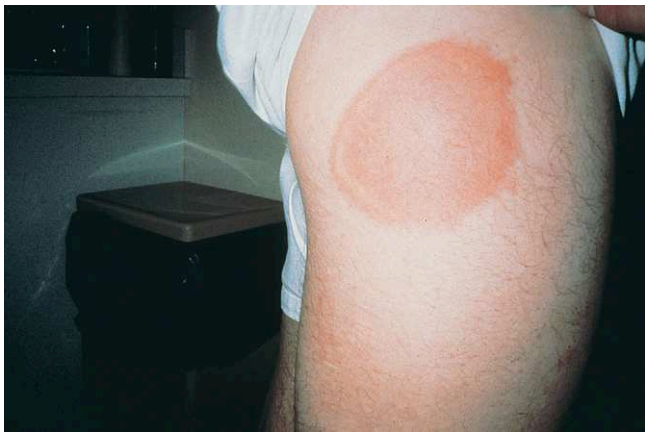

FIGURE 14-20 ■ Lyme disease rash. Note large annular lesion around a central light macule. (From Cohen J, Powderly W: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.)

The bacteria have an affinity for the joints, heart, and nervous system. Bacterial infection of these areas can produce arthralgias, cardiomyopathy, and CNS disorders. Within 1 month of the bite, the patient may notice an expanding skin rash and develop chills, headache, malaise, fatigue, and muscle pain. This is stage 1 of Lyme disease and represents the early, localized disease. The rash, also known as erythema migrans, is bull's-eye shaped, and expands in size to several centimeters. The rash may be well hidden under scalp hair, in the groin area, or on the back of the neck. During this period the patient may get a localized lymphadenopathy and fever.

If left untreated, the patient enters stage 2 of the disease weeks to months after the bite. In this early, disseminated stage the patient may develop a headache with stiff neck and joint pain. The skin may reveal multiple skin rashes distal to the bite. In this stage uveitis is most often seen. More serious manifestations of stage 2 of Lyme disease include meningitis, Bell's palsy, arthritis, and, in 10% of untreated cases, heart abnormalities.

Stage 3 of Lyme disease, or the chronic late-disseminated stage, develops several months to years after the tick bite. This advanced stage may occur in untreated or incompletely treated Lyme disease, and is characterized by knee pain and more CNS complications, including memory loss, hemiplegias, depression, and dementia. Uveitis may also occur in this stage.

The diagnosis of Lyme disease is often made on the basis of signs and symptoms occurring in a patient living in an endemic area. The presence of the erythema migrans skin rash greatly increases the likelihood of the disease. The history of the tick bite in a patient with signs and symptoms of Lyme disease further raises the suspicion of the disease.

Laboratory testing is not necessary in symptomatic patients with tick bite or erythema migrans. In stage 1,

enzyme-linked immunosorbent assay (ELISA) is usually negative, and the symptomatic patient would be treated for Lyme disease anyway. In an asymptomatic patient with tick bite and no rash, ELISA testing may yield a false positive and the patient would receive unnecessary treatment. Lyme-specific indirect immunofluorescence assay (IFA) may be performed in place of ELISA followed by immunoblot testing for IgG or IgM.

In later stages of the disease, polymerase chain reaction (PCR) is used to detect the spirochete in the synovial fluid. If cranial nerve palsy or uveitis is present, a lumbar puncture may detect a CNS infection.

The quick administration of treatment hastens the recovery period, and all patients who display signs or symptoms of Lyme disease should be started on antibiotic therapy. In fact, any patient with a tick bite in an endemic area should receive at least a single dose of 200 mg of doxycycline within 3 days of the bite, because this eliminates almost all risk of infection.

Even if left untreated, however, 85% of patients with stage 1 disease do not go on to develop stage 2 disease. In these cases, the infection is held in check by the immune system.

In nonpregnant adults, the treatment of Lyme disease usually involves the use of doxycycline (100 mg, po bid, for 2 weeks), or, in pregnant women, amoxicillin (500 mg, po tid, for 2 weeks). In children, amoxicillin (50 mg/km/day in 3 divided doses) may be used. Alternatively, adults and children may also use cefuroxime, axetil, or azithromycin.

Patients in the more serious stages of 2 and 3 may require intravenous antibiotics, such as ceftriaxone or penicillin G.

Prevention of Lyme disease transmission is the single most effective way to avoid the effects of this disease. To this end, patients who live in, or are planning to visit, endemic areas, including the northeast and upper Midwestern United States or any forested areas around the world, should be encouraged to wear light-colored clothing to spot the ticks. A full and complete inspection of the skin and hair should be made and any freckle-like lesions evaluated for an embedded tick. Children in particular should be screened for ticks within hours of hiking or playing in tall grass or wooded areas. A shower is recommended within a day of visiting an endemic area. The use of insect spray containing DEET reduces the risk of tick bite. Clothes should be immediately washed after a visit to an endemic area to kill any ticks and prevent transfer of the insect to other people.

Once a tick is found, it should be removed immediately. The longer the tick is imbedded in the dermis, the greater the risk of infection. A jeweler's forceps, or similar implement, should be used to grasp the head of the tick right at the skin level. The body of the tick should never be squeezed as this causes the tick to disgorge its stomach contents into the patient along with the bacteria. The head of the tick should be firmly grasped and rocked gently back and forth until the tick reluctantly pulls out of the skin. This may take several minutes.

After removal of the tick, it may be noticed that some mouth parts are left in the dermis. These are of no concern, although it is advisable to try to remove them. If these are left in the skin it may take longer than 2 years for the mouth parts to eventually work their way out of the dermis.

Syphilis

Known as the "great imposter," this spirochetal infection is a complex systemic illness that may imitate many other diseases. It is caused by *Treponema pallidum,* which belongs to the family Treponemataceae. These bacteria are tightly coiled, slender, unicellular cells that move by a drifting, rotary action.

Syphilis has had a major impact on modern society. For example, this infection was the leading cause of neurologic and cardiovascular disease in middle-aged individuals in the early 1900s. At this time the disease was known as "lues," from the Latin for *lues venereum,* which means "disease," and this term may occasionally be used today.

Syphilis is acquired most commonly by sexual intercourse, although kissing, blood transfusion (rarely), and accidental inoculation may also spread the disease. Congenital syphilis occurs when the fetus is infected in utero, although it is possible for the neonate to acquire the disease during passage through the birth canal.

The disease passes through recognizable stages. After the host is exposed to the spirochetes, *T. pallidum* gains access to the body through breaks in the skin or through intact mucous membranes. Next, it enters the lymphatic or bloodstream and disseminates throughout the body. All organs and tissues of the body may become involved. The first stage of the disease, the incubation stage, lasts for approximately 3 weeks.

After incubation, the disease enters the primary stage. This stage is characterized by the development of a chancre, or primary lesion, at the site of the inoculation (Figure 14-21). Spirochetes can be found in this lesion, though the chancre does not always form or may be hidden from view. These sores heal spontaneously in 2 to 8 weeks, often fooling the individual into thinking that their condition has resolved.

Syphilis then enters the second stage, known as the disseminated stage, 2 to 12 weeks after contact. Manifestations of the disease become apparent at parenchymal and mucocutaneous sites (Figures 14-22 to 14-26). This secondary stage represents a period of highest treponemal load in the skin, bloodstream, and lymph

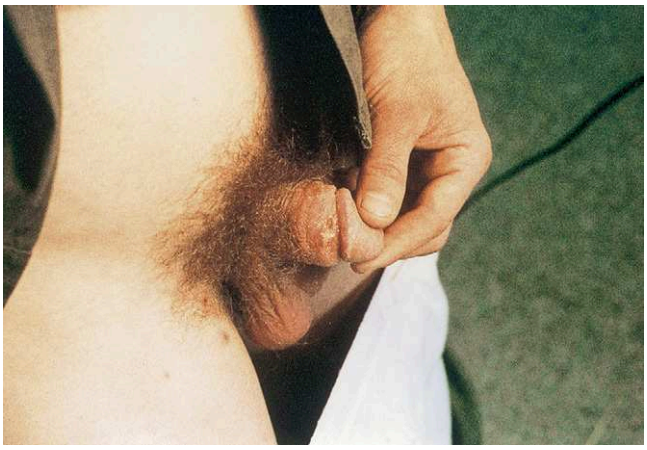

FIGURE 14-21 ■ Primary syphilis. (From Mandell GL, Bennett JE, Dolin R: *Principles and practice of infectious diseases,* ed 6, Edinburgh, 2005, Churchill Livingstone.)

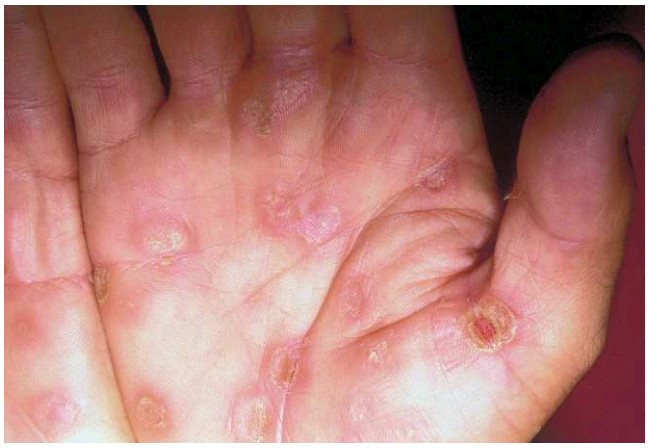

FIGURE 14-24 ■ Palmar lesions of secondary syphilis. (From Mandell GL, Bennett JE, Dolin R: *Principles and practice of infectious diseases,* ed 6, Edinburgh, 2005, Churchill Livingstone.)

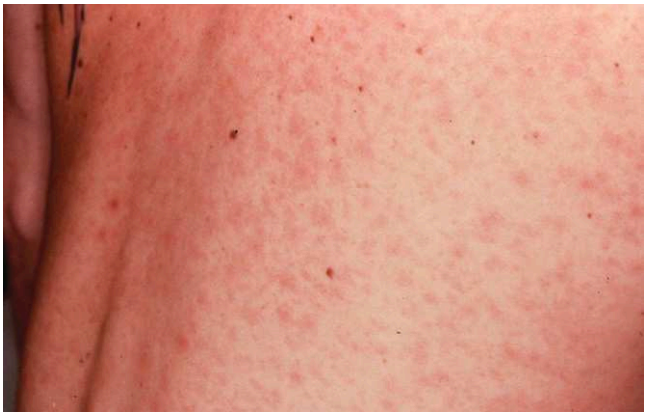

FIGURE 14-22 ■ Rash of secondary syphilis. (From Marx J, Hockberger R, Walls R: *Rosen's emergency medicine: concepts and clinical practice,* ed 6, St Louis, 2006, Mosby.)

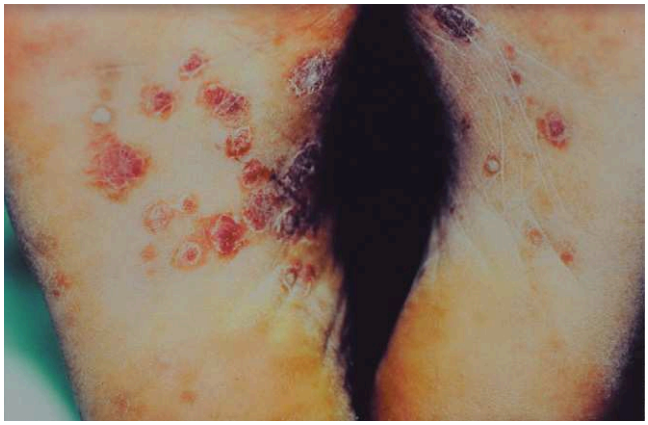

FIGURE 14-25 ■ Cutaneous manifestation. Secondary syphilis on the soles of the feet. (From Marx J, Hockberger R, Walls R: *Rosen's emergency medicine: concepts and clinical practice,* ed 6, St Louis, 2006, Mosby.)

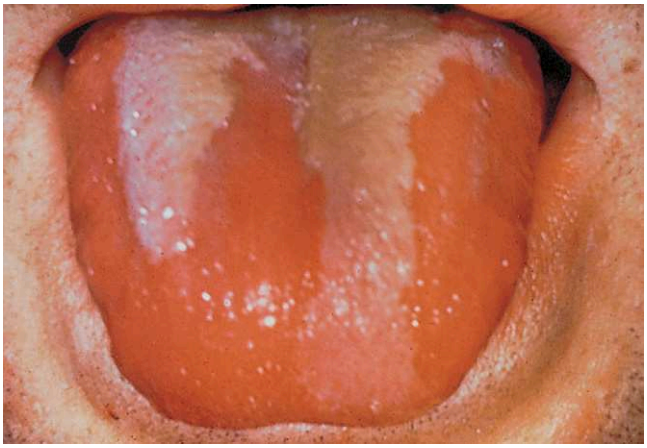

FIGURE 14-23 ■ Secondary syphilis of the mucous membranes of mouth. (From Mandell GL, Bennett JE, Dolin R: *Principles and practice of infectious diseases,* ed 6, Edinburgh, 2005, Churchill Livingstone.)

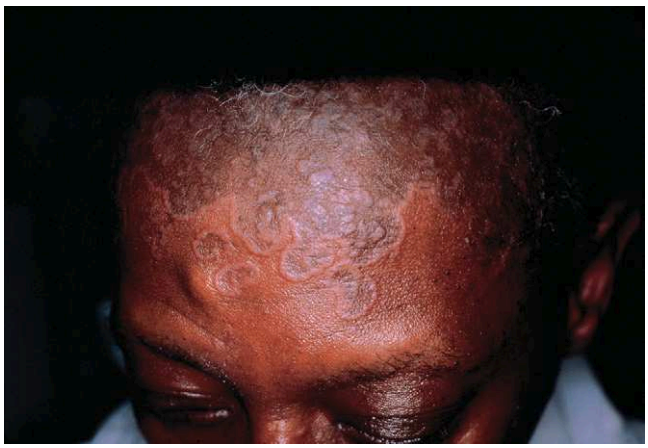

FIGURE 14-26 ■ Less common manifestations of secondary syphilis. Annular plaques of the forrehead with central hyperpigmentation. (From Bolognia JL, Jorizzo JL, Rapini RP: Dermatology, St Louis, 2003, Mosby.)

nodes. In almost half of infected individuals the bacteria can be detected in the CNS and eyes. The immune response in this stage is heightened, and an immune-complex kidney involvement may ensue. The untreated secondary stage subsides after approximately 3 months.

After the secondary stage, the patient enters a latent period during which relapses may occur for the first 4 years, and then become progressively rarer.

Tertiary syphilis, the third recognizable stage of the disease, is also called late syphilis, and occurs in one third of all untreated cases. This stage is characterized by lesions of the aorta and arteries of the CNS. These lesions may also affect skin, liver, bones, and spleen. The lesions, granulomatous in nature and containing a coagulated center, are known as gummas. The gumma is characteristic of late syphilis, but because of effective diagnosis and treatment this lesion is rarely seen today.

Neurologic manifestations may occur at any stage, and are known as neurosyphilis. Clinical manifestations of neurosyphilis include hemiplegia, seizures, speech disturbance, and tabes dorsalis. Tabes dorsalis is a constellation of signs and symptoms that include shooting pains, ataxia, Argyll Robertson (AR) pupils, impotence, constitutional irregularities, peripheral neuropathy, and cranial nerve involvement.

AR pupils are small, irregular pupils that accommodate to near vision but do not react to light. The AR syndrome is characterized by miotic pupils with decreased pupillary light reaction and an intact near response in eyes that have no major vision deficit. AR pupils are typically bilateral, although unilateral cases are known to occur. The AR pupil also dilates poorly in dim illumination.

Congenital syphilis can be completely avoided if the mother is treated within the first 4 months of conception. Congenital syphilis may be acquired in utero by the fetus if the mother is untreated, or by passage through the birth canal. The earliest sign of congenital syphilis is a rhinitis followed by a skin rash on the palms, soles, mouth, and anus. The liver may be heavily infected. If the child survives 1 year untreated, a latent period is entered. During age 5 to 30 years, the patient with congenital syphilis is at extreme risk of developing an interstitial keratitis. Interstitial keratitis is characterized by pain, iritis, photophobia, and superficial and deep vascularization of the corneal stroma. Patients with congenital syphilis may also develop VIII cranial nerve deafness, bilateral knee arthropathy, notched incisors (Hutchinson's teeth), and a "saddle-bridge" nose.

The quickest and most direct laboratory method to establish the diagnosis of syphilis is by darkfield examination or immunofluorescence staining of the mucocutaneous lesions. Treponemes may be identified by the serous transudate of the primary chancre.

Two types of serological tests are used to diagnose syphilis. Two types of antibodies are measured: a nonspecific nontreponemal reaginic antibody and a specific antitreponemal antibody.

Several nontreponemal reaginic tests are used: the venereal disease research laboratory (VDRL), the rapid plasma reagin (RPR) card test, the automated reagin test (ART), or the toluidine red unheated test (TRUST). These are inexpensive, reliable, and easy to perform tests that detect the level of a nontreponemal antibody. Therefore, the tests indirectly detect the population of spirochetes and are effective in measuring the success of therapy. They can determine whether a patient currently has syphilis, but they become nonreactive a year or so after successful therapy. Therefore, nontreponemal tests cannot be used to tell whether a patient has a past history of treated syphilis.

The specific treponemal tests determine the presence of specific syphilis antibodies and are expensive and fraught with false-positive results. They are used to verify nontreponemal results and the two tests are used in tandem. Once positive on a treponemal test, 90% of patients remain positive for their lifetimes. The two treponemal tests are the fluorescent treponemal antibody absorption (FTA-ABS), a standard indirect immunofluorescent antibody test, and the microhemagglutination assay *T. pallidum* (MHATP), which measures specific treponemal antibody.

Treatment for syphilis is based on the stage of the disease. Early, or primary syphilis, is treated with benzathine penicillin G, 2.4 million U, IM, weekly for 2 or 3 doses alone, or with oral regimens. If the patient is allergic to penicillin, doxycycline, 200 mg, po, bid, for 15 days, or tetracycline hydrochloride, 500 mg, po, qid, for 15 days, may be used. In late syphilis, aqueous crystalline penicillin G is delivered IV, or amoxicillin with probenecid may be used.

Chlamydial Infection

Etiology

Chlamydiae are bacteria that possess both RNA and DNA. Three species of *Chlamydia* infect humans, but *Chlamydia trachomatis*, which causes genital and ocular infections, is the most extensively studied. The most common bacterial STD in the United States, *C. trachomatis* causes urethritis, proctitis, and conjunctivitis. Often the condition is asymptomatic. Of patients with Reiter's syndrome, or reactive arthritis (ReA), 70% test positive for *C. trachomatis.* Chlamydial conjunctivitis of the newborn, or inclusion conjunctivitis, causes a mucopurulent discharge 5 to 14 days after birth.

Trachoma is also caused by *C. trachomatis.* This infection produces a chronic conjunctivitis so severe that it has caused more than 20 million cases of blindness

worldwide. Transmission of trachoma occurs from eye to eye by direct contact through hands or contaminated towels. Characteristics include conjunctivitis (Figure 14-27), keratitis with pannus, conjunctival scarring, entropion with trichiasis, and corneal scarring. A dry-eye syndrome results from goblet cell destruction. Treatment includes tetracycline or erythromycin ointment to the eyes. Azithromycin is being evaluated presently as an alternative therapy.

Fungal Infections

Histoplasmosis

This fungal infection is caused by *Histoplasma capsulatum*, a yeast the spores of which are found in soil, particularly near bird and bat droppings. Infection occurs by the respiratory route through inhalation of infectious particles. One example of a histoplasmosis outbreak occurred in the 1990s when a large group of vacationers at a single resort in Mexico became infected. The ultimate source turned out to be soil from an adjacent construction site blown into the air by heavy digging machinery and then inhaled by the tourists.

Once inhaled into the lungs, the fungus can travel through the bloodstream to organs and tissues through the body.

The eyes are significant target organs for the fungus. Active multifocal choroiditis occurs in both eyes, represented by small, active lesions. These active inflammatory areas represent zones of immunological reactions composed of macrophages and lymphocytes. The immune response in these lesions may be so intense that Bruch's membrane becomes damaged, with subsequent alteration of the outer retinal layers and the retinal pigment epithelium (RPE).

After this active phase, the infection establishes a period of dormancy. The fungus may remain quiescent for the rest of the patient's life. In some cases, however, reactivation may occur, with devastating visual results. A macular lesion results in reduced visual acuity and may occur in conjunction with the multifocal choroiditis, leaving peripheral "punched-out" lesions. Peripapillary atrophy completes this classic triad of presumed ocular histoplasmosis syndrome (POHS). Reactivation of the disease can result in subretinal neovascular membrane (SRNVM) growth with a subsequent maculopathy with hemorrhage or retinal detachment. Eventually, the macula scars and results in permanent visual loss.

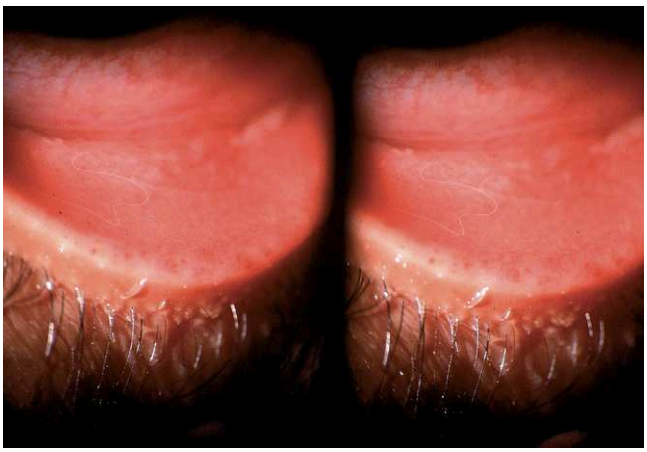

FIGURE 14-27 ■ Chlamydial conjunctivitis, a classic chronic follicular conjunctivitis.

Clinically, patients with POHS only report blurred vision if the macula is involved. Otherwise, a fundus evaluation reveals peripapillary atrophy and chorioretinal atrophic lesions. The macula must be assessed for SRNVM, hemorrhage or RPE detachment.

The retinal presentation of the classic triad of signs is enough to establish the diagnosis of POHS. If there is any suspicion of active maculopathy a fluorescein angiography should be performed to rule-out a SRNVM.

Treatment of SRNVM in POHS involves use of the argon blue-green laser to photocoagulate SRNVMs 200 to 2500 µm from the foveal avascular zone center. In addition, krypton-red laser is used for lesions within 200 µm of the foveal avascular zone.

POHS is found primarily in patients living in or who have recently visited states in the Ohio and Mississippi Valleys. Most common in white individuals aged 20 to 50 years, this condition is found most often in bird handlers who have been exposed to chickens, pigeons, or parakeets.

Mucormycosis

Mucormycosis is a fairly rare fungal infection found primarily in the soil. The fungus mucor is ubiquitous and at any given time almost the entire human population is exposed to it. It becomes opportunistic only in the appropriate environment. The fungus thrives in the blood of the elderly diabetic patient in ketoacidosis, or in those who are immunocompromised. Mucormycosis can be found rarely in young, diabetic drug abusers who inhale, or "snort," poorly prepared, or "cut," cocaine. The impure drug contains the mucor fungus, which is then inhaled directly into the nasal passages and impacts on the mucous membranes. Damaged mucous membranes allow the mucor to gain easy access to the bloodstream. Infection usually causes the demise of the patient who is already ill and febrile from ketoacidosis.

A significant complication of the infection is a mucor invasion of the cavernous sinus. This yields a septic thrombosis with subsequent cavernous sinus syndrome. The patient develops acute and painful diplopia, ophthalmoplegia, dilated pupil, Horner's syndrome, exophthalmos, and conjunctival chemosis. Mucormycosis

has a 90% mortality rate. The skin around the eyes may become necrotic, and the fundus reveals venous stasis retinopathy with "boxcarring," or segmentation, of the blood within the retinal vessels.

The treatment of mucormycosis is problematic because of the rapid spread of the fungus. Patients often demise within 24 to 72 hours despite treatment. Pharmaceutical treatment involves the use of amphotericin B, an antifungal agent. This is a highly toxic agent that in the elderly, febrile diabetic may itself contribute to the patient's demise.

The mucosal membranes rapidly become necrotic. Surgical debridement of these tissues becomes mandatory but is fraught with risks. Of prime importance is the stabilization of the metabolic state. Resolution of the ketoacidosis ensures an environment that is not conducive for mucormycosis, but this must be done quickly and effectively before the patient lapses into a coma.

Protozoan Infections

Toxoplasmosis

This infection is caused by the protozoan *Toxoplasma gondii.* This organism is a parasite that attacks neurologic tissue and has a particular affinity for the retina. Toxoplasma protozoans are found in cats. Infection to the human occurs because of ingestion of uncooked meat or exposure to cat feces. Women may pass the parasites on to the fetus, thus pregnant patients are warned not to change cat litter. Congenital acquired infection can cause ocular and CNS disorders.

When the protozoan infects the retina, a retinitis ensues with white blood cells released from retinal blood vessels. This results in patient complaints of blurred vision and floaters. Fundus evaluation reveals evidence of granulomatous disease. The unilateral involvement produces a large, yellowish-white retinal lesion with an overlying vitritis (Figure 14-28). Older, disciform scars may be adjacent to the areas of involvement (Figure 14-29). Toxoplasmosis also can cause disc edema, retinal vessel occlusion, and iritis. Half of all cases of posterior uveitis are caused by toxoplasmosis. If congenital, the retinal lesion is accompanied by calcification in the brain and central nervous system necrosis.

Congenital toxoplasmosis occurs in 50% of pregnant women infected with the parasite. The first month of pregnancy produces the greatest risk of toxoplasmosis transmission. Toxoplasmosis is transmitted only to the fetus if the mother acquires toxoplasmosis during the pregnancy. If the mother has old toxoplasmosis scars as evidence of congenital infection, she will not pass it on to her fetus. In fact, even if the mother has reactivation of an old toxoplasmosis infection, she will not pass this on to her fetus. She must acquire the infection during the pregnancy to pass it on to the fetus.

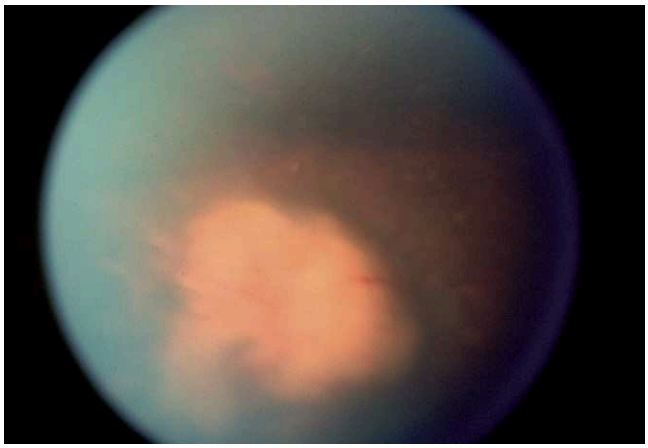

FIGURE 14-28 ■ Toxoplasmic retinochoroiditis. This active lesion obscures the fundus details.

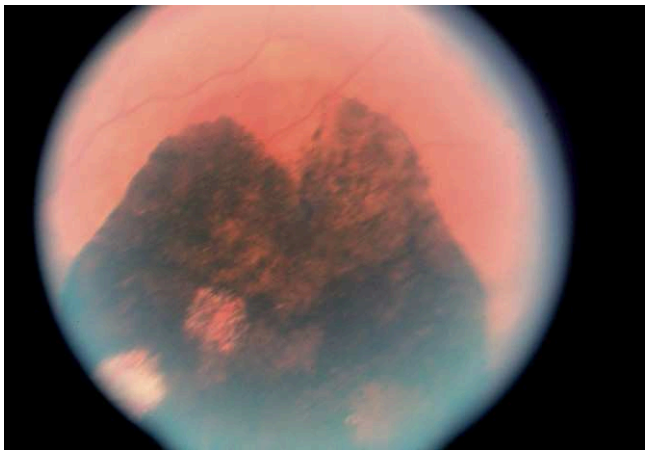

FIGURE 14-29 ■ Toxoplasmosis. Resolution of retinal inflammation results in the formation of discrete, macular, oval pigmented scars with severe loss of central vision.

Treatment begins if the retinitis is near the macula or optic nerve. In addition, therapy is recommended if central acuity is threatened or if a large exudative lesion is present. Treatment uses sulfadiazine with clindamycin and prednisone. Pyrimethamine (Daraprim) is concurrently used with these medications. Folinic acid is also administered to prevent drops in the white blood cell count. A combination drug, trimethoprim and sulfamethoxazole (Septra DS), replaces the sulfadiazine and pyrimethamine and folinic acid regimen.

Toxocariasis

Toxocariasis represents an infection in the human by the larval stage of the parasite *Toxocara canis.* This roundworm infects the intestinal tract of dogs and the toxocariasis eggs are released into the dogs' feces. Once in the soil, the eggs are viable for years.

Infection of the human occurs by direct ingestion of the eggs when soil accidentally enters the mouth. Once the eggs enter the human intestine they hatch into larvae that quickly pass through the mucosal wall and migrate to target organs and tissues.

Once the toxocariasis larvae arrive at the end organ, they produce a granulomatous inflammation characterized by the release of eosinophils. The white blood cells fragment the larvae, the remains of which are found in the granuloma.

Toxocariasis is typically a disease of a child younger than 10 years who has a habit of putting his or her fingers in the mouth. The child may suffer fever, cough, skin rash, and abdominal pain. Ocular involvement produces a white pupil and strabismus. In the eyes, granuloma formation and endophthalmitis may be present.

The signs and symptoms of toxocariasis are so self-evident that laboratory testing is usually unnecessary. ELISA testing for toxocara antibodies is highly sensitive and specific, however.

No treatment is available for toxocariasis and the disease is self-limiting. Subretinal larvae may be destroyed by laser therapy.

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CHAPTER 15

Hematology and Oncology

CHAPTER OUTLINE

HEMATOLOGY

Blood Cell Production

The highly regulated and tightly controlled production of blood cells is known as hematopoiesis (Table 15-1). Environmental demands, such as infection, allergy and hemorrhage, stimulate rapid and appropriate changes in white and red blood cell (RBC) levels.

Stem Cells

Primitive forebears known as stem cells produce all blood cells. Stem cells are located in the adult mammalian bone marrow. Highly mobile cells, stem cells can transform rapidly into a variety of blood cells. A stem cell passes through a cell cycle during which it can differentiate into several different cell types under the influence of colony-stimulating factor (CSF), although the regulation of stem-cell plasticity is poorly understood.

Stem Cell Microenvironment

The primitive stem cell is renewed and proliferates under the influence of the local microenvironment. Tissues that surround the stem cell contain macrophages, fibroblasts, endothelial cells, and smooth muscle cells. These cells communicate with and stimulate the stem cell by the release of cytokines.

Cytokines

Cytokines are glycoproteins that play a role in cell-to-cell communication. Cytokines are produced by cells in the plasma cell microenvironment in response to an induction signal. The cytokines act in low concentrations on stem cells to stimulate or inhibit such processes as stem cell renewal, proliferation and function. Examples of cytokines include erythropoietin (for red blood cells), and thrombopoietin (for platelets).

Cytokine Therapy

Cytokine therapy is a newer form of treatment in many clinical settings. For example, when tissue becomes hypoxic, the kidneys produce erythropoietin. Patients in chronic renal failure may benefit from erythropoietin treatment. Cytokine therapy is also being evaluated in cases of HIV/AIDS, neutropenia, malignant melanoma, lymphoma, multiple sclerosis, and metastatic and lung cancer.

Disorders of the Blood

The Anemias

Anemia can be the result of several factors, including a decrease in the number of circulating erythrocytes, or a reduced hemoglobin amount. The pathophysiology of anemia lies in the failure of the bone marrow to produce RBCs because of such deficiencies as iron or B_{12}, hemolysis secondary to drugs, and antibody formation. Whatever its cause, anemia is one of the most common disorders seen by the primary care physician. Whenever the clinical sign of the anemia is established, it is important to determine the underlying cause. Possible causes include blood loss (for instance, from gastrointestinal cancer), iron deficiency, nutritional deficiencies, hemolysis secondary to drugs, antibody formation, and chronic disease states (such as end-stage renal failure).

TABLE 15-1 BLOOD CELL VALUES IN A NORMAL POPULATION

	MEN	MEN AND WOMEN	WOMEN
White cell count, x 10^9/L blood		7.8 (4.4-11.3)	
Red cell count, x 10^{12}/L blood	5.21 (4.52-5.90)		4.60 (4.10-5.10)
Hemoglobin, g/dl blood	15.7 (14.0-17.5)		13.8 (12.3-15.3)
Hematocrit, ratio	0.46 (0.42-0.50)		0.46 (0.36-0.45)
Mean corpuscular volume, fl/red cell		88.0 (80.0-96.1)	
Mean corpuscular hemoglobin, pg/red cell		30.4 (27.5-33.2)	
Mean corpuscular hemoglobin concentrations, g/dl RBC		34.4 (33.4-35.5)	
Red cell distribution width, CY (%)		13.1 (11.5-14.5)	
Platelet count, x 10^9/L blood		311 (172-450)	

Anemia Symptoms

The symptoms of anemia vary depending on its cause. Severe blood loss may produce acute anemia and the associated clinical signs and symptoms of shock, overall weakness, and postural hypotension. Chronic anemia produces feelings of fatigue, dyspnea, palpitations, and angina. Some mild anemias produce no symptoms and are found only on laboratory testing.

Classification of the Anemias

Anemia is best classified by the underlying pathophysiologic mechanism combined with RBC morphology and survival. Anemias may therefore be the result of decreased production of RBCs (secondary to nutritional deficiency or chronic disease) or increased destruction of RBCs (secondary to drugs, trauma, or intrinsic hereditary defects). The morphologic classification of anemia involves cell size and color. An anemia characterized by large RBCs is therefore known as macrocytic anemia. An anemia characterized by normal RBCs is normocytic, and if small RBCs are present, then the anemia is microcytic. If the RBCs are of normal color then the anemia is normochromic. If the RBCs are pale, then the anemia is hypochromic. The morphologic description of the anemia helps determine the type of anemia, its treatment, and prognosis.

Diagnosis

Once anemia is clinically suspected, it can be confirmed by laboratory testing, including a complete blood count (CBC), hemoglobin and hematocrit (H & H), RBC count, white blood cell (WBC) count, a differential, and RBC indices. A reticulocyte count helps determine the bone marrow's capacity to respond to anemia by increasing erythrocyte production. To detect morphologic changes of the erythrocyte, a peripheral blood smear is examined.

Ocular Manifestations of Anemia

The eye is a unique avenue to visualize the effects of anemia. The cardinal symptom of conjunctival pallor, usually expressed when the red blood cell count is 50% of normal, is a variable clinical finding. Anemic retinopathy is characterized by flame-shaped or dot-and-blot hemorrhages. In addition, intraretinal hemorrhages surrounding a white center (Roth's spots) may also be present depending on the level of anemia. When the anemia has occurred rapidly or is extremely severe, cotton-wool retinal exudates (nerve-fiber layer infarcts) may also be visualized. The tortuosity of the retinal vessels varies inversely with the level of anemia. In rare cases, papilledema occurs associated with a type of pseudotumor cerebri precipitated by cerebral anoxia. In patients with only anemia, and no other blood abnormalities, only 10% exhibit anemic retinopathy with hemorrhages. But if the anemia coexists with thrombocytopenia, then 40% to 70% of patients will exhibit retinal hemorrhaging. Retinal hemorrhaging is rare in patients with thrombocytopenia alone. The frequency of hemorrhage depends therefore on whether the anemia coexists with thrombocytopenia.

Hypoproliferative Anemias

The most common of all anemias, these disorders are caused by iron deficiency, malignancy, inflammation, and renal disease. Anemia caused by iron deficiency (the most common form) is characterized by a reduced concentration of hemoglobin with hypochromic, microcytic (pale, small) erythrocytes. Iron deficiency may occur in pregnancy, adolescence, disease states, and hemorrhaging. Anemia causes the typical symptoms of anemia including fatigue, skin pallor, and a reduced capacity to exercise. Laboratory testing can determine iron deficiency by testing serum iron level and the total iron-binding capacity. Most cases of iron-deficiency anemia can be treated with oral iron therapy. The underlying cause of the iron deficiency should be determined and

appropriately managed, however. Hemorrhaging with subsequent anemia and cardiovascular involvement may require red cell transfusion.

Other causes of hypoproliferation anemias include inflammation, infection, and renal disease. Chronic diseases often cause anemia and recovery of normal hemoglobin levels occurs when the underlying disease is managed. Although anemia caused by iron deficiency is the most common form of anemia, chronic disease states cause the second most common type of anemia. Anemias caused by chronic disease states are characterized by normochromic, normocytic RBCs and are hypoproliferative in origin. They are commonly caused by chronic renal failure, chronic liver disease, and endocrine dysfunction. Specific therapy for anemia of chronic disease is not necessary because it resolves with successful treatment of the associated disorder.

Megaloblastic Anemias. These hypoproliferative anemias are the result of a deficiency of folic acid, vitamin B_{12}, or both. This deficiency causes impaired DNA synthesis. The cells produced are large, with more RNA than DNA, and RBC production in the bone marrow is decreased. Anemia caused by iron deficiency (the most common form) is characterized by a reduction in hemoglobin with hypochromic, microcytic (pale, small) erythrocytes. Cobalamin, or vitamin B_{12}, deficiency commonly causes pernicious anemia. This condition is a disease of the elderly with a mean patient age of approximately 60 years. Pernicious anemia results from an absence of intrinsic factor (IF), which is a cell-directed carrier protein for cobalamin. Autoimmune disease is thought to play a role in cases of abnormal or nonexistent IF. Treatment is highly effective and usually results in normal lifelong correction of the anemia. The treatment of cobalamin deficiency is replacement therapy by using intramuscular cyanocobalamin every month for the rest of the patient's life. Oral vitamin B_{12} supplementation may also be effective. Folate deficiency is treated by oral replacement.

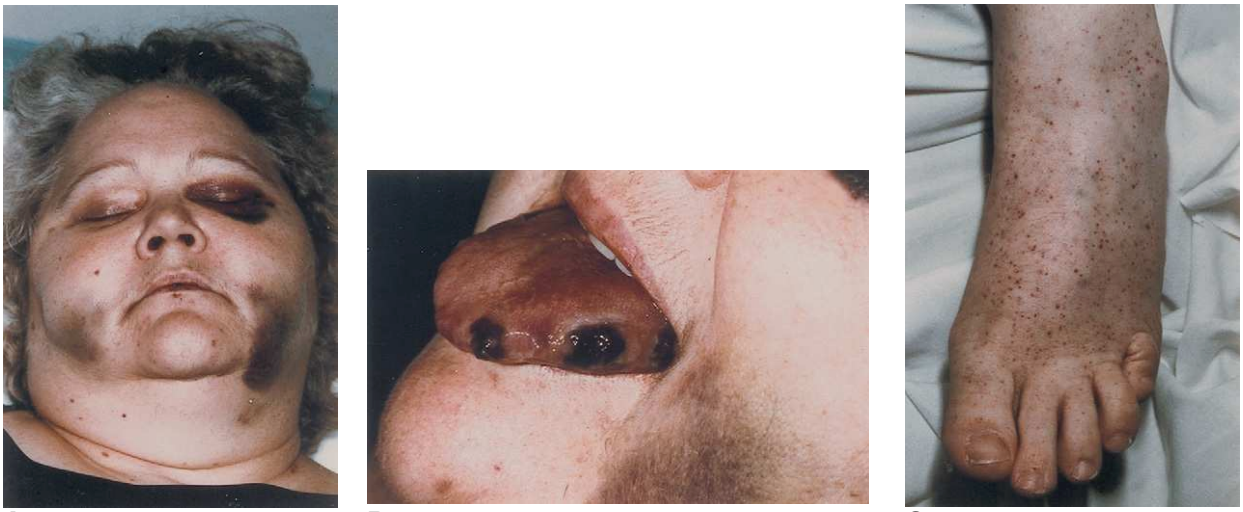
Hemolytic Anemias. These hypoproliferative anemias result from premature destruction of the RBC (hemolysis) or by hemorrhage. These both cause an increase in RBC production and an increase in reticulocytes, the immature RBCs. The signs and symptoms are vague and usually involve fatigue, jaundice, and red-brown urine. The causes of hemolytic anemia include inherited inborn deficiencies in the RBC membrane, enzymes, or hemoglobin; RBC enzyme defects, and toxic or antibody damage to the circulating RBC.

One example of a hemolytic anemia is thrombotic thrombocytopenia purpura (TTP). TTP is the prototypical nonimmunological anemia characterized by destruction of the platelets. In this condition platelet thrombi aggregate in the arterioles of various organs and cause RBC fragmentation. This activation of platelets causes a microangiopathic hemolytic anemia with thrombocytopenia. This reduction in platelets and RBCs results in tissue hypoxia, most commonly in the kidneys and central nervous system (CNS). TTP usually occurs in young adult women who are seen with fever and anemia. Laboratory tests reveal reduced renal function and neurologic findings include confusion and delirium. Eventually, seizures, hemiplegias, and visual field defects may result. Other ocular manifestations include extraocular muscle palsies and papilledema. A TTP retinopathy may occur consisting of hemorrhages and serous detachments secondary to focal occlusion of the choriocapillaris. Retinal pigment epithelial damage may result, with disruption of the blood-retinal barrier, and coma and death may occur. Therapy requires immediate plasma exchange, and plasmapheresis treatments may be required for months.

Immune-mediated mechanisms may also cause thrombocytopenia. This disorder is a common cause of accelerated platelet destruction because of production of antiplatelet antibodies. Idiopathic thrombocytopenic purpura (ITP) occurs in children after a viral infection, or in young and middle-aged women as a chronic disease. ITP is associated with production of antibodies against platelet antigens. ITP may cause intracranial hemorrhage. The ocular findings associated with ITP include retinal hemorrhages and an association with Graves' disease.

Another type of immune-mediated thrombocytopenia occurs after exposure to certain drugs. Such drugs may include quinine, quinidine, sulfonamides, heparin, phenytoin, diazepam, and acetaminophen. The ocular effects associated with drug-induced thrombocytopenia include subconjunctival and vitreous hemorrhages, bilateral serous retinal detachments, and disc edema.

Aplastic anemia (AA) is a hypoproliferative anemia associated with bone marrow damage. The reticulocyte count is low in AA, and the anemia is not a major finding. Rather, the bone marrow failure is significant and results in reduction in all types of blood cells. AA is typically devastating because of the inability of the bone marrow to produce some or all peripheral blood elements. AA typically occurs in healthy, young individuals with an abrupt onset of low blood cell counts. It is characterized by normocytic or macrocytic RBCs combined with a very low reticulocyte count. The cause is unknown, although marrow aplasia occurs because of radiation exposure, benzene exposure, chemotherapeutic drugs, and hepatitis. Early in the disease patients complain of easy bruising (Figure 15-1) and nose bleeds. Patients may experience weakness and dyspnea, but look remarkably well. The treatment of AA involves a complete cure with stem cell transplant. The best therapy is bone marrow transplant



A B C

FIGURE 15-1 ■ Clinical presentations of aplastic anemia. **A**, Ecchymosis in pancytopenic women. **B**, Submucosal hematomas. **C**, Petechial eruptions in a thrombocytopenic patient. (From Hoffman R: *Hematology: basic principles and practice*, ed 4, Edinburgh, 2005, Churchill Livingstone.)

from a compatible donor. Immunosuppression aids recovery in approximately half of cases.

Fanconi's syndrome is congenital AA. The disease can best be described as severe pancytopenia-depression of the hemoglobin, WBC, and platelets, or any combination thereof, within the first 6 weeks of life. In addition to retinal findings of flame-shaped hemorrhages, associated with thrombocytopenia, a platelet count of less than 20,000/dl is usually present. Patients may also be seen with congenital cataracts.

Hemoglobinopathies

These disorders of the red blood cell affect the structure, function, or production of hemoglobin. Hemoglobin functions to deliver oxygen to tissues and any alteration in this molecule can produce anemia. Such alterations include RBC structural changes, RBC death, and abnormal oxygen-carrying capability.

The prototypical hemoglobinopathy is sickle-cell anemia (SCA). A single mutation in the beta-globulin gene results in the formation of fibrous polymers that causes a gelatinous erythrocyte membrane. Under anoxic conditions, sickle cell hemoglobin is relatively insoluble, and the molecules accumulate in parallel rows within the red cell. The stiffened RBC membrane causes the cell to assume a sickle shape. The sickled cell cannot easily pass through the small capillary lumen and it tends to stick to endothelial walls. This results in microvascular occlusion and RBC destruction. Tissue ischemia results from clogged capillaries and produces painful episodes characterized by fear, anxiety, and muscular pain. These painful crises last from hours to days and may occur anywhere in the body. Tissue destruction may lead to end-organ destruction. Infarction of the skin, spleen, CNS, bones, liver, and lungs may occur. SCA may cause renal necrosis and renal failure. Stroke may also occur and is usually the result of cerebral hemorrhage rather than infarct. Sickling of red cells with abnormal hemoglobin occurs under conditions of decreased oxygen tension, a condition seen more often in organs with more sluggish circulation, such as the spleen, gastrointestinal (GI) tract, lungs, joints, and bones.

The origin of the sickled gene can be traced to the African continent. Data suggest that this mutation of the hemoglobin chain protected those affected from malaria infestation. Genetically, valine is substituted for glutamic acid, causing a structural deformity of the hemoglobin chain. This structural abnormality causes the hemoglobin chain to form crystals, accounting for the sickle-shape red blood cell that leads to intravascular clotting.

The frequency of the sickle cell gene is approximately 12% in the American population. It encompasses individuals of African American, Mediterranean, Middle Eastern, and Southeast Asian ancestry in descending order of frequency. Normal adults inherit two genes that code for normal adult hemoglobin (AA). The abnormal hemoglobins are inherited as autosomal dominants; consequently, individuals who have at least one gene coding for normal adult hemoglobin (A) therefore have the trait (AS only, known as sickle cell trait, and being heterozygous with 50% hemoglobin C or S) and rarely have complications. Patients with hemoglobin SS (homozygous with both parents having the disease and classified as sickle-cell

anemia), manifest the worst systemic symptomology but not the most severe ocular complications. When the sickled hemoglobin is combined with other abnormal hemoglobins (thalassemia, sickle hemoglobin C, hemoglobin E), ophthalmic pathology may be expected in the second decade of life. Patients with sickle cell hemoglobin C and S-beta thalassemia hemoglobinopathies exhibit the most severe ocular complications.

Orbital involvement of SCA includes the symptom of pain and the sign of proptosis. SCA causes a retinopathy by occlusion of the retinal vessels. This results in hemorrhage and eventual retinal neovascularization in a "sea fan" appearance. Repeated vitreous hemorrhages may result in fibrovascular scarring and retinal detachment. The ophthalmic pathologic changes can be categorized as follows:

1. Superficial changes, as evidenced by comma-shaped vessels seen in the conjunctiva. These background changes are nonproliferative, and are evidenced by venous tortuosity, vascular loops, schisis, cotton-wool spots, and angioid streaks.

2. Nonproliferative retinal hemorrhages that may be preretinal, intraretinal, or subretinal in location. As these hemorrhages resolve, various signs occur depending on the depth of retinal involvement. These findings include salmon patches (retinal hemorrhages with partially degenerated blood), retractile deposits (iridescent spots that represent old, resolved, subinternal limiting membrane hemorrhage with hemosiderin deposition), and black sunbursts (resulting from a retinal hemorrhage that extends to the subretinal space and causes secondary retinal pigment epithelial hyperplasia with migration into the retina in a perivascular location). The nonproliferative findings rarely affect vision and consequently require no treatment.

3. A proliferative retinopathy that usually affects the retinal periphery and, because of its progressive nature, is associated with visual loss.

Proliferative SCA consists of the following five stages:

Stage I: Peripheral arteriolar occlusions
Stage II: Peripheral AV anastomoses
Stage III: Neovascularization in a "sea-fan" appearance
Stage IV: Vitreous hemorrhage
Stage V: Traction or rhegmatogenous retinal detachment

The diagnosis of abnormal hemoglobin may be suggested by abnormal red-cell morphology (sickle cells, target cells, hemoglobin crystals in the cytoplasm). The diagnostic clinical test is hemoglobin electrophoresis, which not only confirms the presence of abnormal hemoglobin but also quantitates the specific amounts. This quantitation can frequently aid in the clinical and prognostic decisions in this disease. SCA is always suspected in an anemic patient with ischemic pain, and hemoglobin electrophoresis and sickling tests confirm the diagnosis.

The treatment of SCA includes narcotic analgesia to control the painful crises. Routine optometric examinations are necessary to evaluate and monitor any SCA retinopathy. Photocoagulation as well as retinal surgery has been used to stabilize the retinal lesions associated with SCA. Peripheral neovascularization (seafans) has been reported to spontaneously regress 50% of the time. The proliferative findings are most consistently associated with individuals who have hemoglobin C (AC, SC, CC). Long-term medical care is necessary to manage the typical causes of SCA morbidity: end-stage renal failure and pulmonary hypertension.

The thalassemias are syndromes that result from genetic defects that produce unstable globin chains that cause damage to the RBC membrane. This problem leads to hemolysis. Two forms of thalassemia exist: beta-thalassemia major (Cooley's anemia) and alpha-thalassemia.

Beta-thalassemia is a severe form of the disease and is usually fatal in childhood. It is diagnosed by the findings of microcystic, hypochromic RBCs combined with other specific test results. The disease may present as a homozygous beta-thalassemia or a heterozygous form. This type of patient has beta-thalassemia trait, which is usually free of symptoms. Genetic counseling is of utmost importance to these individuals. Therapy for beta-thalassemia major includes frequent transfusions and iron chelation (to remove excess iron). Homozygous alpha-thalassemia results in intrauterine demise. The heterozygous form should be suspected in Asians with hypochromic, microcytic anemia without iron deficiency. Special testing is necessary in these individuals.

Chronic Myeloproliferative Disorders

One of the most common chronic myeloproliferative disorders is polycythemia vera. This disorder is characterized by overproduction of one of the formed elements of the blood. An increase occurs in RBCs, granulocytes, and platelets. The etiology is unknown, although it appears related to stress, high altitude, chronic lung disease, tumors, and kidney disease. Diagnosis is made on review of the hematocrit level. The elevation in the mass of RBCs leads to systemic hypertension and venous thrombosis. Blood viscosity increases, causing retinal hemorrhaging, transient blindness (amaurosis fugax), and blurred vision. The retinal pathology is associated with red cell counts in excess of 6 million/mm^3, and is characterized by marked dilation and tortuosity of the retinal vessels with severe stasis retinopathy. Superficial and deep retinal hemorrhages may occur with associated swelling of the optic nerve head. Ultimately there may be retinal venous and artery occlusion. Uric acid levels increase causing gout and pruritus. Treatment

makes use of phlebotomy, radioactive phosphorus, and alkylating agents, to reduce the hyperviscosity of the blood.

Blood viscosity may also be influenced by plasma proteins and produce a range of disorders known as serum protein abnormalities. Three categories of plasma proteins circulate with the liquid fraction of blood: albumin, fibrinogen, and several types of globulins. Diseases associated with protein abnormalities can be primary or secondary (Table 15-2). The ophthalmic pathology is that of a congestive retinopathy. Waldenström's macroglobulinemia and myeloma have been associated with this pathology. The laboratory findings, in addition to a variable level of anemia, are an abnormal protein electrophoresis with the characteristic "M" protein spike.

Coagulopathies

The flow of blood has a regulatory mechanism to retard or stop the egress of the precious fluid. This system is called the coagulation or clotting system. The production, destruction, and quality of its components and the number and quality of the circulating platelets regulate bleeding. The clotting cascade is a complex scheme that explains the sequential steps in the intrinsic and extrinsic clotting system. A disorder at any point in this system is called a coagulopathy, and examples include hemophilia, hypercoagulable syndromes, and disseminated intravascular coagulation.

Hemophilia

The more severe coagulopathies are usually sex-linked and therefore have their greatest expression in males (hemophilia A and B). The more frequent bleeding diatheses are associated with deficiencies of those factors made by the liver. Accurate diagnosis requires the interpretation of the prothrombin time, activated partial thromboplastin time, platelet count, and specific assays where indicated. Treatment is with specific replacement of the factor by human blood products or synthetic derivatives. Intraocular or extraocular hemorrhage may occur spontaneously, by trauma, or during surgery. Bleeding most commonly occurs 24 to 36 hours after the trauma. Most hemorrhages are self-limiting, but some require treatment. Retrobulbar hemorrhage may cause central retinal artery occlusion.

Hypercoagulability Syndromes

In the past two decades the clinical presentation of hypercoagulable syndromes has been better described. The circulation of activated clotting factors could result in uninhibited intravascular clotting (usually venous). The critical inhibitors of this coagulation are antithrombin III, protein C, and protein S. Congenital deficiency states have been associated with ophthalmic thrombotic complications (1 in 500,000 live births).

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a dynamic hematologic state in which, because of the underlying processes, clotting occurs throughout the body, with consumption of clotting substances in excess of the body's ability to replenish the consumed substances. DIC is characterized by activation of the coagulation system, consumption of coagulation proteins and platelets, and thrombic occlusion of the small blood vessels. DIC is usually an acute emergent process associated with thrombocytopenia, prolonged prothrombin time, prolonged activated partial

TABLE 15-2 ELECTROPHORESIS OF SERUM AND URINE PROTEINS IN DISEASES ASSOCIATED WITH PROTEIN ABNORMALITIES

CLINICAL INDICATIONS	ABNORMALITY AND INTERPRETATION
Unexplained edema or ascites	Hypoalbuminemia
Suspected liver disease	Hypoalbuminemia frequent; hyperglobulinemia suggests cirrhosis or chronic active hepatitis
Collagen diseases, sarcoidosis	Polyclonal hyperglobulinemia
Unusual susceptibility to infections	Hypogammaglobulinemia or agammaglobulinemia
CLL, malignant lymphoma	Hypogammaglobulinemia or, rarely, IgG or IgM M components
Unexplained proteinuria	Albumin or a mixture of all serum proteins is found with urinary tract infections or the nephrotic syndrome; homogeneous urine proteins that migrate in the globulin region are usually indicative of plasma cell neoplasms secreting free light or heavy chains.
Evidence of plasma cell neoplasms (e.g., bone pain, frequent infections, elevated sedimentation rate, rouleaux formation, proteinuria, or osteolytic skeletal lesions)	Serum or urinary monoclonal protein, with reduced normal immunoglobulins and hypoalbuminemia
Amyloidosis	Monoclonal serum or urinary proteins frequent

thromboplastin time, low fibrinogen level, and fragmented RBCs on the peripheral smear. Clinically, widespread hemorrhage and ischemic tissue damage is present. No test is available to confirm the diagnosis. With a rapidly evolving clinical picture and generalized bleeding, however, a high index of suspicion is the single most important factor in proper diagnosis and treatment. Although the recommendations for treatment are varied, none is successful unless the underlying mechanism is controlled. Ocular involvement in DIC can include retinal pigment epithelium necrosis and serous retinal detachments resulting from thrombic occlusion of the choriocapillaris and larger choroidal vessels. Visual loss occurs when the submacular choroid is affected. DIC may be confused with TTP, because both entities are characterized by thrombocytopenia. Only in DIC, however, does widespread activation of coagulation and fibrinolysis exist. Coagulation tests are therefore abnormal in DIC and are unaffected in TTP.

Leukemia

This group of diseases is characterized by infiltration of the blood and bone marrow by neoplastic blood cells, and is a malignancy of the blood-forming organs. Malignant proliferation of WBCs or any of their developmental forms is called leukemia. Eye signs occur in 50% to 70% of cases of leukemia. Known as myeloid leukemia, this disorder can be seen as acute or chronic forms. Acute myeloid leukemia (AML) is caused by radiation, chemical exposure, or hereditary factors. Two forms exist: the lymphoid (L1, L2, and L3) and nonlymphoid (ANLL, M1-M7) varieties (Table 15-3). Symptoms include fatigue, weakness, anorexia with weight loss, bleeding, HA, and bone pain. The mass lesion associated with AML is a granulocytic sarcoma and is composed of leukemic cells. Clinical signs include anorexia, GI bleeding and enlarged spleen.

The initial presentation of AML may relate to a visual complaint. Ophthalmoscopic findings in cases of AML include retinal infiltrates and papilledema. The optic nerve head swelling can occur because of leukemic infiltration of the optic nerve. In fact, leukemic infiltrates may be seen additionally in the retina, choroids, or vitreous. Ocular infiltrates are associated with a poor prognosis for life when found with high WBC counts, and fulminant disease. Cranial nerve palsies may occur because of CNS leukemia. Emergent triage to a subspecialist conversant in the management of leukemia is paramount to the patient's survival. Leukemia is an ocular emergency until proven otherwise. Treatment is aimed at complete remission (CR) and prolongation of survival. CR is achieved by combination chemotherapy. No cause has been found for chronic myeloid leukemia (CML), in which presenting symptoms are vague. CML affects the lymphoid or the myeloid cells. Patients complain of fatigue and weight loss, with a much more insidious onset than AML. Eventually, fevers occur with continued weight loss. The spleen is found to be enlarged on physical examination. Lab findings including the CBC and bone marrow tests demonstrate elevated WBCs. Treatment of CML involves a bone marrow transplant from an HLA-compatible donor. Both AML and CML may have an associated leukemic retinopathy. When found in the context of anemia, thrombocytopenia, and increased blood viscosity, retinal hemorrhages may occur in the posterior pole. These can be flame-shaped or dot-and-blot hemorrhages. In addition, Roth's spots may occur in leukemia. The white area found central in a Roth spot is composed of platelets and fibrin.

TABLE 15-3 CLASSIFICATION OF ACUTE LEUKEMIA

TYPE	FAB* CLASSIFICATION	FREQUENCY (%)	CASES/YEAR (U.S. CHILDREN YOUNGER THAN AGE 15)
ALL			1,500-2,000
AML	LI	85	
	L2	14	
	L3	I	
AML			
AML	MI	20	400-500
AML with differentiation	M2	20	
APML	M3	3	
MMMol	M4	25	
AMOL	M5	26	
Erythroid leukemia	M6	4	
Acute megakaryocytic leukemia	M7	2	

*French-American-British
ALL, Acute lymphoblastic leukemia; *AML,* acute myelogenous leukemia; *APML,* acute promyelocytic leukemia; *MMMol,* acute myelomonocytic leukemia.

Cotton-wool spots may also occur in leukemic retinopathy in the absence of systemic symptoms. Often the finding of cotton-wool spots motivates the eye examiner to order the systemic work-up that ultimately leads to the diagnosis of leukemia.

Lymphoma

Malignancies of the lymphoid cells always present as leukemia of the bone marrow and blood or as a lymphoma. A lymphoma is a solid tumor of the immune system. Lymphoid malignancies have been classified into three types by the World Health Organization: the non-Hodgkin's lymphomas (B-cell and T-cell neoplasms), and Hodgkin's disease. Lymphoma is the most common malignancy that infiltrates the optic nerve. Usually lymphomatous cells infiltrate the retrolaminar portion of the optic nerve. Visual analysis will confirm the presence of a relative afferent papillary defect, color and visual field defects, and a painless reduction of visual acuity, all on the involved side. Ophthalmoscopy may reveal disc edema caused by the infiltrative optic neuropathy. Radiotherapy can be used in the treatment of infiltrative optic neuropathy secondary to lymphoma

Hodgkin's Disease

HD occurs at a rate of approximately 8000 cases per year in the United States. The most common presenting symptom is a nontender, palpable lymphadenopathy in the neck. Some patients exhibit fever, night sweats, and weight loss. Confirmation of the disease is made by lymph node biopsy. More than 90% of patients with HD are cured by extended-field radiotherapy, although chemotherapy is traditionally used first. This treatment is then followed by radiotherapy to the involved nodes.

ONCOLOGY

Systemic Cancer

The Cancer Patient

The diagnosis of cancer, regardless of the type or prognosis, is often a life-altering experience for the patient. The patient often feels emotions of guilt, depression, and anxiety. The cancer patient often feels that they could have done something to prevent the disease, and their lifestyle is often forever altered.

Epidemiology of Cancer

In 2000 more than a million new cases of invasive cancer were diagnosed in the United States, and in the same year more than a half million patients died of some form of cancer. It is the second leading cause of death in the United States after heart disease. The incidence of cancer increases dramatically with age, the most significant cancer risk factor. The leading cause of cancer deaths in both men and women is primary tumor of the lung. The second most common cause of cancer death in men is primary tumor of the prostate, and in women it is breast cancer. The third most common cause of cancer death is colorectal cancer, followed by pancreas and then, in men, lymphoma, and in women, primary tumor of the ovary. In men the most common form of cancer is primary tumor of the prostate (30%), followed by lung cancer (15%), colorectal cancer (10%), bladder cancer (6%), and lymphoma (5%). In women the most common form of cancer is primary tumor of the breast (30%), followed by lung cancer (12%), colorectal cancer (11%), endometrial cancer (6%) and ovarian cancer (4%).

Diagnosis of Cancer

The diagnosis of cancer mandates tissue biopsy because no noninvasive test can confirm the disease. Beyond prevention, successful management of cancer relies heavily on early and accurate diagnosis. Once identified, the extent of the disease is determined by defining its clinical stage.

Cancer Treatment

The most effective treatment of cancer is surgical excision, accounting for a 40% cure rate. At least 60% of all solid tumors, however, can have associated metastatic disease. Radiation therapy makes use of a characteristic of tumor cells making them more sensitive to the lethal effects of radiation than normal tissue cells. Chemotherapy uses chemicals to stimulate tumor regression or to slow tumor growth. Cancers considered possibly curable by chemotherapy include Hodgkin's disease and certain lymphomas. Chemotherapy and radiation are both used to treat breast cancer, uterine carcinoma and small cell lung carcinoma. Advanced tumors poorly responsive to chemotherapy include melanoma and pancreatic cancer, renal, thyroid, and prostate carcinoma.

Side Effects of Cancer Treatment

Cancer therapies are toxic and produce physical and psychosocial challenges. Side effects of treatment include pain, nausea, vomiting, anorexia, weight loss, and recurrent infections. Cancer therapy must address these unacceptable, life-threatening side effects. Chemotherapy commonly causes nausea and vomiting. Prochlorperazine is given to prevent emesis and may be enhanced by intravenous dexamethasone. Agents may be given to prevent emesis because this is more effective than alleviation of vomiting once it has started.

Goals of Cancer Treatment

Ideally, a complete response to therapy occurs wherein the disease completely resolves. Progressive disease is established on the appearance of a new lesion or an increase in the size of the tumor of more than 25%.

Tumor Markers

Tumor markers are used in some cases to gauge response to therapy. These markers include hormones, oncofetal antigens, enzymes, and tumor-associated proteins. For example, catecholamines are hormones used in the detection of pheochromocytoma, and prostate-specific antigen (PSA) is a prostate cancer-associated protein.

Cancer Pain

Cancer-related pain is most often the result of invasion of the bone, nerves, or mucous membranes, by the tumor itself. Surgical or medical procedures related to cancer treatments account for approximately one fifth of all cancer-related pain. Mild pain is often controlled with NSAIDs, acetaminophen, or aspirin. Persistent or severe pain may mandate the use of codeine, oxycodone, or morphine. Nutritional advice and psychosocial support are both essential elements in the successful management of cancer patients, and should be offered in all cases of the disease.

Cancer Prevention

Cancer prevention is a field that identifies biologic, genetic, and environmental influences that stimulate and promote cancer production, and develop interventional strategies to manipulate and minimize the impact of these factors.

Risk Factors

The most avoidable cancer risk is smoking. The optometrist can and should counsel any known patient who smokes on the benefits of smoking cessation. Changes in diet may reduce the risk of cancer. Patients should be counseled to lower dietary animal fat intake and to increase consumption of foods rich in anticarcinogenic compounds including the phenols, flavones, and fiber found in fruits, nuts, and vegetables. Avoidance of sun exposure and specific carcinogenic chemicals including asbestos, arsenic, benzene, and vinyl chloride, may reduce the risk of cancer. In addition, certain infections, including Epstein-Barr virus, hepatitis, HIV/AIDS, and *Helicobacter pylori* are associated with specific cancer types. In the spring of 2006, a vaccine was approved to prevent the viral etiology of cervical cancer.

Intraocular Tumors

Metastatic tumors to the eye are increasing in incidence because of the increasingly prolonged survival of cancer patients. The most common form of intraocular malignant tumor is metastatic cancer. The incidence of ocular metastases is approximately 300,000 per year. These tumors are often not found because they occur primarily in terminally ill patients who do not seek optometric evaluation. Only approximately 5% of ocular tumors are considered primary to the eye. The remaining 95% occur by metastasis or direct extension. The nonmetastatic ocular pathophysiology is that of infection (Box 15-1). Host immunosuppression caused by the underlying malignancy predisposes the host to opportunistic infections that are primarily viral, fungal, or protozoan. These infections are extremely difficult to treat and invariably need the recommendations of an infectious disease specialist to avoid catastrophic blindness (Box 15-2).

Metastases to the eye occur only in adults and are more common in women because of breast cancer, and in men because of lung cancer (Table 15-4). In children, metastases are very rare. The most common tumor to metastasize to the eye is the carcinoma. In 90% of cases of intraocular metastasis, the primary site is found by clinical evaluation.

The macula is the most common site in the eye for metastatic tumor involvement. Metastasis to the retina, optic disc, or vitreous is rare. Macular involvement demonstrates a painless loss of vision and the discovery of a choroidal tumor in the posterior pole. The

BOX 15-1
OPHTHALMIC MANIFESTATIONS OF SYSTEMIC CANCER

Metastatic
Orbit
Ocular
- Anterior segment
- Posterior segment

Nonmetastatic
Infections
Treatment-related complications
Remote effects (paraneoplastic)

BOX 15-2
COMMON OCULAR INFECTIONS IN CANCER PATIENTS

Anterior Segment
Herpes zoster (iritis, keratitis)
Herpes simplex (iritis, keratitis)

Posterior Segment
Toxoplasmosis (retinitis)
Cytomegalovirus (retinitis)
Herpes simplex (retinitis)
Fungal infections
- Candida species (retinitis)
- Mucormycoses (vasculitis)

Endogenous Endophthalmitis
Bacterial
Fungal

TABLE 15-4 MOST COMMON PRIMARY CANCERS IN CHOROIDAL METASTASES

PRIMARY CANCER	% CHOROIDAL METASTASES
Breast	71.8
Lung	8.9
Genitourinary	3.2
Gastrointestinal	2.4
Gynecologic	1.6
Sarcoma	1.6
Other	10.0

metastatic tumor of the choroids is typically single or multiple creamy-yellow lesions deep to the retina. No inherent pigment is present, but the overlying RPE may be disrupted. An associated nonrhegmatogenous retinal detachment may be associated with the tumor. Metastatic tumors may be bilateral and multifocal. The diagnosis of metastatic choroidal tumor is aided by fluorescein angiography, ultrasonography, intraocular biopsy, and systemic evaluation. Treatment of choroidal metastatic tumor includes external beam radiotherapy and chemotherapy. Treatment of the primary tumor is usually associated with regression of the ocular metastases. The prognosis in patients with metastatic carcinoma to the choroid is generally quite good. The systemic prognosis is guarded.

Ocular Tumor Detection

Intraocular tumors, whether primary or the result of metastatic extension, may be suspected on the basis of the following six characteristics (Figures 15-2 and 15-3):

1. Increase in size. Suspicious lesions of the eye or adnexa may be visualized grossly or require diagnostic techniques. These approaches include direct ophthalmoscopy, indirect ophthalmoscopy, stereoscopic ophthalmoscopy (with 60, 75, or 90 diopter lens and biomicroscope), and gonioscopy. Tumors of the ciliary body may be visualized by retroilluminating the sclera with a bright penlight placed near or on the limbus 180 degrees away from the suspected lesion. Whatever technique is used, the lesion must be described as well as possible, drawn, measured accurately, and, if possible, photographed. Photographic alternatives include standard slit-lamp or retinal cameras, stereoscopic cameras, digital photography and videography. The suspicious lesion should be remeasured at regular intervals. Growth raises the possibility that the lesion is malignant.
2. Discoloration. In general, a lesion is more suspicious for malignancy if it reveals a discoloration compared with the normal surrounding tissue. Discoloration is just one small piece of evidence that suggests a serious disorder; of course, many discolored ocular lesions are benign.
3. Neovascular growth. Vascular changes may occur to a greater degree within or overlying intraorbital tumors than in benign lesions. Any lesion that is associated with a dilation of surrounding normal vasculature (for example, on the conjunctiva) or is associated with neovascular growth should be evaluated for possible malignancy. Intraocular tumors may produce vascular abnormalities as visualized on fluorescein angiography. They may hyperfluoresce, hypofluoresce, or be "invisible" to the test, depending on the nature of the choroidal tumor.
4. Indistinct margins. In general, benign ocular tumors tend to have distinct margins, whereas malignant lesions have indistinct margins. This difference results from the malignancy growing and spreading through the surrounding tissue. The

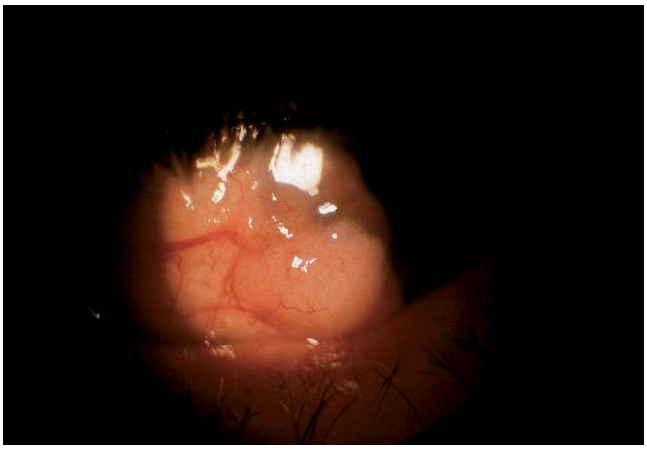


FIGURE 15-2 A preoperative view of a conjunctival tumor which was suspicious because of increasing size, discoloration (from normal conjunctival tissue), surrounding engorged blood supply, indistinct margins, distortion of surrounding conjunctiva and induced astigmatism causing a loss of visual function.

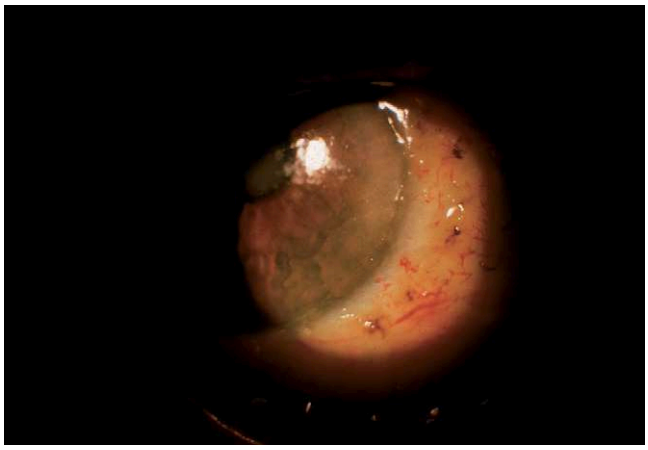


FIGURE 15-3 The postoperative appearance of the same patient as in Figure 15-2. Biopsy revealed a primary conjunctival malignancy.

tumor border may reveal both lateral spread and deep-tissue invasion.

5. Distortion of the surrounding tissue. A malignant tumor has a greater tendency to distort the normal tissue surrounding it than does a benign growth. Again, this is the result of lateral and deep spread of the malignancy through the tissues around it. Also, metastatic islands of spread may be detected visually around the main lesion.
6. Loss of function. In general, benign lesions cause little or no loss of normal organ function. Malignant tumors have a greater potential for interfering with ocular function. An iris melanoma may therefore cause a papillary anomaly; a ciliary body tumor may alter aqueous production and, hence, intraocular pressure; and a choroidal malignancy may be associated with a serous detachment and possible loss of vision.

Management of Ocular Malignancy

The management of both ocular metastases and primary ocular malignancies may include irradiation of the eye or surrounding tissue. Ophthalmic consequences may be immediate: dry eye, corneal ulceration, delayed cataract, neovascularization, ischemic ocular syndrome, neovascular glaucoma, and optic neuropathy secondary to radionecrosis. The prolonged survival of the cancer patient can also be associated with neuroendocrine syndromes related to tumor kinetics, toxins, antibodies, nutritional deprivation, or tumor hormone elaboration (Box 15-3). These are extremely unusual syndromes, and the occurrence of this pathology indicates a need for further evaluation for a primary cancer. The ocular complications from systemic or local (regional) chemotherapy are constantly increasing (Boxes 15-4 and 15-5). Complete medical history is the single most important factor in minimizing the impact of these drugs.

The ophthalmic consequences of systemic cancer require continuing dialogue and early referrals of the eye-care professional and the practicing oncologist. When they work together, the life and vision of the cancer patient may be significantly prolonged.

BOX 15-3
REMOTE EFFECTS OF CANCER IN THE VISUAL SYSTEM: VISUAL PARANEOPLASTIC SYNDROMES

Ocular
Optic neuritis
Photoreceptor (retinal) degeneration (melanoma, oat-cell carcinoma)

Oculomotor
Opsoclonus (breast cancer, lung cancer)
Opsoclonus-myoclonus syndrome (neuroblastoma, thyroid, breast)
Lambert-Eaton myasthenic syndrome

BOX 15-4
OCULAR COMPLICATIONS OF SYSTEMIC CHEMOTHERAPY

Lids
5-Fluorouracil (entropion)
Vincristine (ptosis)
Vinblastine (ptosis)

Conjunctiva (Conjunctivitis)
5-Fluorouracil
Methotrexate
Melphalan
Cyclophosphamide

Lens (Cataract)
Busulfan
Corticosteroids
Mitotane

Optic Nerve (Optic Neuritis)
Vincristine
Cisplatin
Nitrosourea (BCNU)

Lacrimal System
5-Fluorouracil (ductal fibrosis)

Cornea (Keratitis)
Busulfan
Chlorambucil
Cytarabine

Uvea
BCG
Thiotepa

Retina
Mitotane
Tamoxifen (refractile deposits)
Chlorambucil (hemorrhage)
Cisplatin
Nitrosourea (BCNU)

BOX 15-5
OCULAR SIDE EFFECTS OF INTRAARTERIAL CHEMOTHERAPY

Intracarotid Nitrosourea
Local pain (eye, orbit)
Conjunctivitis
Keratitis
Disc edema
Optic neuritis
Ocular ischemia and neovascularization
Retinal degeneration (vasculitis)

Intracarotid Cisplatin
Optic neuritis
Transient visual loss
Retinal degeneration, with characteristic photopic electroretinographic changes
Toxic neuroretinitis
Pigmentary changes in retina, constricted arterioles, pale nerve

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CHAPTER 16

Dermatology*

CHAPTER OUTLINE

TERMINOLOGY

The presence of a skin lesion should prompt the examiner to make every effort to correctly describe it in appropriate dermatological terminology (Box 16-1). Lesions may be flat or elevated, and may be solid or filled with pus, fluid, or blood vessels.

Flat lesions of less than 2 centimeters are called macules, and they are typically colored. A classic example of a macule is a freckle. A larger, flat and colored lesion is called a patch. A patch is a large macule and a typical example is vitiligo.

Descriptors of raised skin lesions are based on size and content. The smallest elevated lesion, known as a papule, is less than a centimeter in size and is solid in nature. Unlike a macule, a papule is palpable. A typical example of a papule is the raised lesion characteristic of acne rosacea. If the papule is filled with keratin, then it is known as milia. If the small lesion is fluid filled it is referred to as a vesicle (Figure 16-1). Vesicles are the translucent lesions produced in cases of contact dermatitis from exposure to poison ivy. If the small lesion is filled with pus, it is referred to as a pustule (Figure 16-2). These lesions are filled with leukocytes. Cysts are raised lesions filled with fluid or semisolid contents.

A nodule is a solid, elevated lesion, similar to a papule, but measuring from 1 to 5 centimeters in size. A bulla is a fluid-filled nodule. An elevated lesion larger than 5 centimeters is known as a tumor.

If the elevated lesion is larger than a centimeter and has a flat, plateau-like top, then it is referred to as a plaque. This is the typical lesion that characterizes psoriasis and eczema. If the plaque is erythematous, it is referred to as a wheal, and is caused by dermal edema.

A painless, elevated overgrowth of dilated and superficial blood vessels is known as telangiectasia.

DERMATOLOGICAL PROCESSES AND SYSTEMIC CONSIDERATIONS

Certain processes are unique to dermatological conditions, and their appearance aids in identification, diagnosis, prognosis and treatment. Most often, but not

*Special thanks to David C. Bright, author of the dermatology chapter in the first edition of this book. Many of his photographs and tables are reprinted in this edition.

BOX 16-1
TYPES OF SKIN LESIONS

Primary Lesions
Macule: Circumscribed, flat discoloration, variety of colors.
Papule: Circumscribed, solid, elevated lesion; as large as 5 mm in diameter; variety of colors.
Nodule: Circumscribed, solid, elevated lesion; larger than 5 mm in diameter.
Tumor: Large nodule.
Pustule: Circumscribed collection of leukocytes and free fluid.
Vesicle: Circumscribed collection of free fluid, as large as 5 mm in diameter.
Bulla: Circumscribed collection of free fluid, larger than 5 mm in diameter.
Plaque: Circumscribed, elevated, superficial, solid lesion; larger than 5 mm in diameter; often formed by confluence of multiple papules.
Wheal: Firm, edematous plaque; caused by infiltration of the dermis by fluid.

Secondary Lesions
Scale: Excess dead epidermal cells, resulting from abnormal keratinization and shedding.
Crust: Dried serum, cellular debris (scab).
Erosion: Focal loss of epidermis; no penetration beyond dermis.
Ulcer: Focal loss of epidermis and dermis.
Fissure: Linear loss of epidermis and dermis; sharply defined walls.
Atrophy: Depression in the skin, caused by thinning of epidermis or dermis.
Scar: Abnormal collection of connective tissue; damage to dermis.

Special Lesions
Excoriation: Erosion resulting from scratching.
Cyst: Circumscribed lesion with a wall and lumen.
Lichenification: Thickened epidermis caused by scratching; furrowed surface (washboard).
Telangiectasia: Dilated superficial capillaries or blood vessels.
Comedones: Sebaceous and keratinous material plugging the opening of a hair or sebaceous follicle.

Adapted from Habif TP: *Clinical dermatology,* ed 2, St Louis, 1990, Mosby-Year Book.

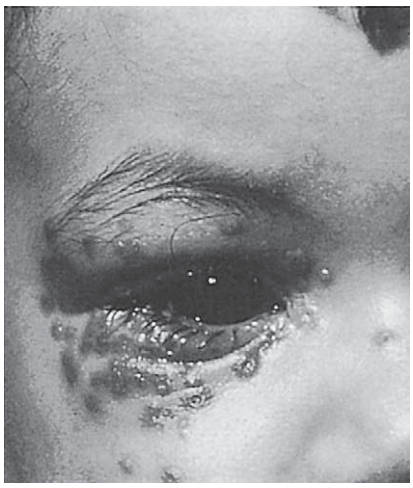

FIGURE 16-1 Primary herpes simplex infection, with uniformly sized vesicles on an erythematous base.

always, topical lesions are inflammatory in nature and cause erythema, or reddening of the skin. Also common is the production of pruritus, a strong desire to scratch. Pruritus is typical of inflammatory skin conditions, such as allergic contact dermatitis.

The skin may erode, and such erosions represent a loss of epidermal tissue without loss of underlying dermis. If the dermis and epidermis both are eroded, an ulcer forms. If an underlying loss of substance causes the intact epidermis to become depressed, this is referred to as atrophy.

Trauma and inflammation may result in scar tissue formation, a condition in which the skin is permanently changed.

Flat lesions involve the processes described in the text that follows.

Erythroderma

When the skin is reddened because of an inflammatory response, the resulting condition is referred to as erythroderma. Erythroderma is caused by a dilation of local blood vessels, thus, the area will blanch with pressure. Erythematous skin conditions are often associated with overlying erosions, pustules, and scales. The most common causes of reddened skin are cutaneous diseases, including the various types of dermatitis and psoriasis. If the reddened skin is associated with overlying plaques and located on the elbows and knees, then psoriasis should be suspected. Drug-induced erythroderma can be caused by the penicillins, sulfonamides, phenytoin, allopurinol, and captopril. An associated constellation of clinical signs including fever, chills, and lymphadenopathy is not unusual. The presence of such signs and symptoms in the context of erythroderma indicates a possible underlying systemic condition. The most common malignancy to cause erythroderma is T-cell

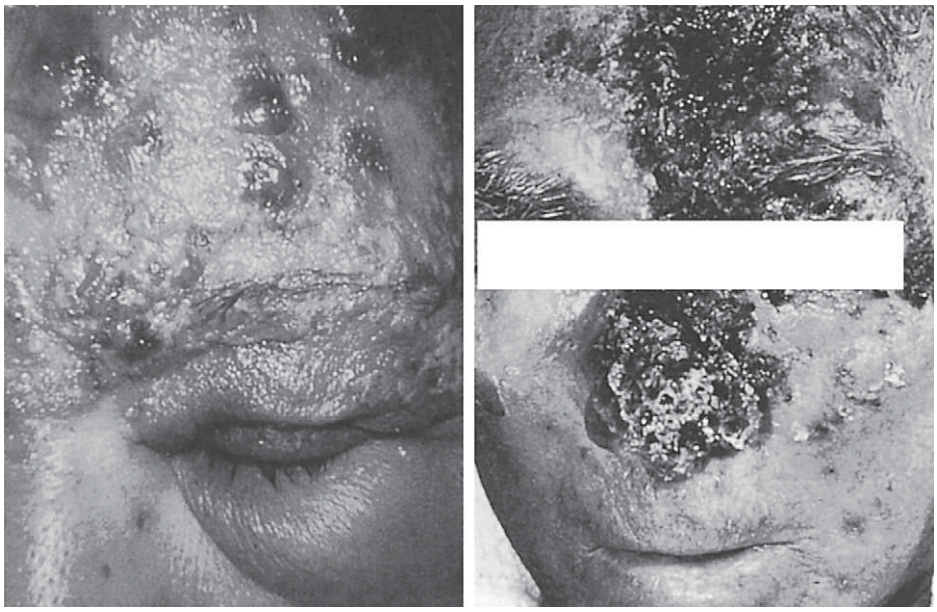

FIGURE 16-2 ■ **A,** Herpes zoster ophthalmicus, with vesicular and pustular eruptions. **B,** Herpes zoster ophthalmicus, with extensive crusting.

lymphoma. In summary, when a patient is seen with an isolated area of erythematous skin involvement, in most cases it is the result of psoriasis or dermatitis. A detailed medical history should uncover any new medications the patient ingested just before the outbreak of reddened skin. If the erythroderma occurs in conjunction with any systemic signs or symptoms, an immediate medical work-up should be done to test for an underlying systemic pathology.

Figurate Skin Lesions

These erythematous skin lesions form rings or arcs, are flat and nonpalpable, and are typically red, brown, or flesh-colored. A classic example is erythema migrans, the skin rash associated with Lyme disease. This annular lesion is usually larger than 10 centimeters in diameter and is usually associated with systemic manifestations of the disease including fever, headache, photophobia, and myalgias. Syphilis is another systemic disease associated with classic figurate skin lesions, which, in this case, manifest typically on the palms of the patient's hands and soles of the patient's feet.

Hypopigmentation

Loss of skin pigmentation can be diffuse, bodywide, or localized. Oculocutaneous albinism (OCA) is the classic example of diffuse hypopigmentation. OCA is caused by a mutation in the tyrosinase gene. In these individuals bodywide distribution of melanocytes is present with a lack of tyrosinase enzyme activity. This results in the white hair, gray-blue eyes, and pinkish-white skin characteristic of OCA. A defect in the *P* gene produces partially expressed OCA. Significant ocular findings are present in OCA patients including strabismus, amblyopia, nystagmus, and photophobia. The prototypical local hypopigmented lesion is vitiligo, which produces a patchy loss of pigmentation. In vitiligo an absolute loss of melanocytes is present within the patch.

Hyperpigmentation

Like hypopigmentation, hyperpigmentation can be diffuse or localized. The localized forms of hyperpigmentation are caused by either a proliferation of melanocytes or an increase in pigment production. The sudden onset of multiple pigmented skin lesions may point to an underlying malignancy, usually in the gastrointestinal (GI) tract. Proliferation of melanocytes may be benign, resulting in melanocytic nevus, or malignant, resulting in melanoma. Systemic medications such as nonsteroidal antiinflammatory drugs (NSAIDs), sulfonamides, barbiturates, and antimalarials can cause localized hyperpigmentation. Hyperpigmentation may occur in Addison's disease, hyperthyroidism, and Cushing's disease.

Alopecia

Hair loss may be caused by an elevation in circulating androgen hormone in women and should prompt a diligent medical workup for ovarian or adrenal gland tumor. Alopecia is a frequent side effect of medications,

including vitamin A, isotretinoin, lithium, beta-blockers, amphetamines, and the blood thinners warfarin and heparin. Systemic diseases such as lupus erythematosus, thyroid disorders, sarcoidosis, HIV/AIDS, and syphilis may be an underlying cause of alopecia.

Nonpalpable Purpura

This condition is caused by the leaking of red blood cells into the dermis. Purpura will not blanch with pressure. Trauma and sunburn are the two most common causes of nonpalpable purpura. Systemic conditions that cause thrombocytopenia and abnormal platelet function will cause nonpalpable purpura. In addition, patients on blood thinning agents tend to develop nonpalpable purpura, even with minor trauma. Nonpalpable purpura is the cause of the classic "shiner" resulting from blunt trauma to the periorbital area. The resulting extravasation of red blood cells into the soft, thin tissue surrounding the eye produces a typical "black and blue" bruising of the skin. After immediate evaluation for orbital fracture, traumatic uveitis, hyphema, retinal detachment, and globe perforation, treatment of uncomplicated periorbital purpura involves cold compresses to reduce periorbital swelling. The patient should be advised that it can take longer than 1 month for the periorbital purpura to completely resolve.

Elevated lesions involve the processes described in the text that follows.

Urticaria

These transient lesions, more commonly known as hives, are composed of an erythematous ring surrounding a central wheal (Figure 16-3). They are invariably pruritic and often provoke an intense desire to scratch. An outbreak of hives may be very short-lived and persist for no longer than 10 to 20 minutes. In other cases urticaria can persist for such a long time that it becomes chronic. The most common cause of hives (Box 16-2) is an allergic response. Urticaria is also often provoked by exposure to heat, cold, and sunshine. Exercise and emotional stress are also related to the production of small wheals. Systemic diseases that may underlie urticaria include hyperthyroidism, malignancy, and juvenile rheumatoid arthritis. Any outbreak of hives coincident with a fever should

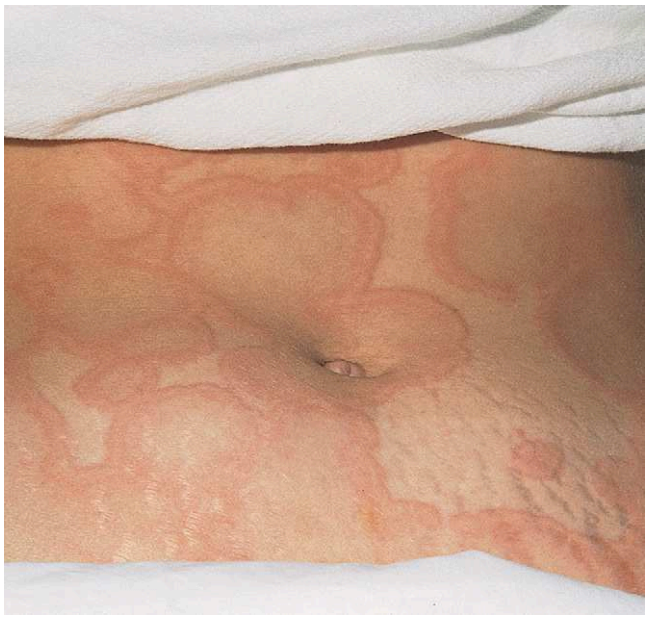

FIGURE 16-3 Urticaria, with multiple hives of varying sizes. (From Noble J: *Textbook of primary care medicine,* ed 3, St Louis, 2001, Mosby.

BOX 16-2
CAUSES OF URTICARIA

Food: Fish, shellfish, nuts, eggs, chocolate, strawberries, tomatoes, pork, cow's milk, cheese, wheat, yeast.
Food additives: Salicylates, benzoates, aspartame (NutraSweet), dyes such as tartrazine.
Drugs including penicillin, aspirin, sulfonamides.
Infections of varying microbial causes:
- Chronic bacterial (sinus, dental, chest, urinary tract)
- Fungal (dermatophytosis, candidiasis)
- Viral (hepatitis B prodromal reaction, infectious mononucleosis)
- Protozoal and helminthic (intestinal worms, malaria)

Inhalants: Pollen, mold spores, animal danders, dust mites, aerosols, volatile chemicals, nasal sprays, insect sprays, feathers.
Internal disease including serum sickness, systemic lupus erythematosus, hyperthyroidism, carcinomas, lymphomas, juvenile rheumatoid arthritis, polycythemia vera, rheumatic fever.
Physical stimuli: Dermatographism, pressure, exercise, water, solar exposure, temperatures (heat and cold).
Nonimmunologic contact: Nettles, jellyfish, some medications (cinnamic aldehyde, compound 48/80, DMSO).
Skin diseases: Urticaria pigmentosa, dermatitis herpetiformis, pemphigoid, amyloidosis.
Hormones: Pregnancy, premenstrual flare-ups (progesterone).
Insect bites and stings: Mosquitoes, flies, spiders, caterpillars.
Psychogenic stimuli: Nervous stress, worry, fatigue.

Adapted from Habif TP: *Clinical dermatology,* ed 2, St Louis, 1990, Mosby-Year Book; and from Sauer GC: *Manual of skin diseases,* ed 5, Philadelphia, 1985, JB Lippincott.

prompt an immediate medical evaluation for an underlying systemic disease.

Angioedema

Subcutaneous edema typically involves the skin of the eyelids and lips. Angioedema may occur with or independent of urticaria. Angioedema presents as well demarcated, localized edema deep in the skin (Figure 16-4). Precipitating factors (Box 16-3) include inhalation of animal dander and plant pollen, and ingestion of allergenic foods and drugs. Angioedema of the upper respiratory tract may be life threatening. In angioedema the deeper layers of the skin become inflamed and inundated with lymphocytes, eosinophils, and neutrophils. The local venules dilate, causing the classic ruddy color of the skin. Treatment of angioedema is predicated on the identification and removal of the offending agent, the use of systemic antihistamines and, in severe cases, systemic glucocorticoids.

Papulonodular Lesions

These conditions involve elevated and palpable lesions that coalesce to form plaques. The diagnosis of a papulonodular lesion is made primarily on the basis of color and secondarily on location.

FIGURE 16-4 ■ Angioedema of the eyelid.

BOX 16-3
CAUSES OF ANGIOEDEMA

Severe allergy reactions (type I): Food, drugs, stinging insect venom, pollen.
Contrast dyes and aspirin caused by direct histamine release rather than immune mechanism.
Serum sickness after exposure to the following elements:
- Heterologous serum
- Animal-derived vaccines
- Drugs (penicillin, sulfonamides, thiouracils, aminosalicylic acid, streptomycin, hydantoins, cholecystographic dyes)

Adapted from Habif TP: *Clinical dermatology,* ed 2, St Louis, 1990, Mosby-Year Book.

Skin-Colored Lesions

These lesions include inclusion cysts, lipomas, rheumatoid nodules, basal cell carcinomas, and neurofibromas.

Yellow-Colored Lesions

Typically papules or plaques, these yellow-colored lesions are often caused by systemic conditions. One of the most common of the yellow lesions is the xanthoma, which is often related to hyperlipidemia.

Purple-Colored Lesions

Kaposi's sarcoma may be associated with cutaneous, purple-colored papules and plaques. These represent vascular tumors and their presence should prompt a diligent search for HIV infection.

Red-Colored Lesions

Insect bites often result in a reddened papule. Small, bright-red and dome-shaped papules are most often cherry hemangiomas, however, that represent benign overgrowth of capillaries. Large red plaques often form across the nose and cheeks in the classic butterfly rash associated with lupus erythematosus.

Red-Brown–Colored Lesions

Sarcoidosis can produce cutaneous lesions that are red-brown in coloration. These papules or plaques occur most commonly on the face.

Pustular Dermatoses

These eruptions of pustules are most often associated with acne and are associated with the bacteria *Staphylococcus aureus* and the yeast *Pityrosporum.* The use of systemic steroids has been linked to a bodywide pustular outbreak.

Vesicular Dermatoses

Cutaneous blisters may occur in immunologically mediated skin conditions such as pemphigus vulgaris. Contact dermatitis may stimulate the formation of vesicles, and drug sensitivity may cause bullae formation characteristic of Stevens-Johnson Syndrome (SJS), or erythema multiforme major.

SELECTED FLAT SKIN LESIONS

Vitiligo

This acquired and progressive cutaneous disorder is characterized by a complete absence of melanocytes within the affected area. The condition produces symmetric and extensive areas of chalky, white depigmentation, most commonly around the eyes and lips and on the distal extremities. Vitiligo is associated with

such autoimmune disorders as hypothyroidism, Graves' disease, pernicious anemia, and Addison's disease. Approximately one third of patients with vitiligo have thyroid gland abnormalities, and laboratory testing in these patients usually reveals antithyroid-globulin, a circulating autoantibody. The treatment of vitiligo is problematic, but patients are typically upset about their perceived cosmetic appearance. Topical glucocorticoids are useful in cases with a mild associated inflammatory condition. UV-B light treatments have met with some limited success in reducing the overall depigmented appearance of the skin. The presentation of vitiligo should prompt a diligent medical search for the associated condition of Vogt-Koyanagi-Harada syndrome (VKH). VKH encompasses the clinical signs of facial vitiligo in a patient with meningitis, granulomatous uveitis, tinnitus, and hearing loss. In VKH an underlying autoimmune disease is directed against the melanocytes of the skin and the uveal tract. The most common symptoms associated with VKH are blurred vision, ocular pain, photophobia, a stiff neck, and nausea. Clinical signs of VKH include vomiting, syncope, alopecia, and hearing loss. VKH is most common in Japan, in women, and in young adults aged 20 to 50 years. The treatment of VKH includes topical steroids and cycloplegic agents to manage the granulomatous uveitis, and cytotoxic agents such as cyclosporine for the systemic manifestations of the disorder. A retinal referral for fluorescein angiography is mandatory in VKH to monitor for retinal atrophy and choroidal involvement.

Erythema Multiforme Minor

This cutaneous condition is characterized by one or more sharply demarcated erythematous lesions in response to an ingested drug. The lesions are known as target or iris lesions. The lesions are most commonly found on the face, lips, hands, legs, or oral mucosa. An associated burning of the skin and sore throat with malaise may be present. Repeated ingestion of the drug will tend to cause repeated outbreak of the erythematous lesions in the same location. The most common drugs that elicit this reaction include NSAIDs, sulfonamides, and barbiturates. The lesions disappear with discontinuation of the inciting medication. Should a worsening of the skin condition occur on discontinuation of drug, with blistering and a systemic mucosal reaction, then Stevens-Johnson Syndrome (SJS) must be considered.

Sturge-Weber Syndrome

This congenital cutaneous condition is characterized by one or more flat, well-demarcated reddish-purple facial lesions. Known as "port-wine staining" this skin condition results from capillary venous angiomas of the face and is usually present at or shortly after birth. The angiomas in SWS always follow the distribution of the first branch of the trigeminal nerve (V1), and may involve branches V2 and V3 as well. SWS is part of a broader group of disorders known as the phakomatoses, the typical characteristics of which include cutaneous lesions and neurologic abnormalities. In SWS, benign facial skin angiomas are present that may also be present in the choroid of the eyes and in the meninges of the brain. Complications arise caused by the presence of choroidal angiomas that result in glaucoma, and meningeal angiomas that result in childhood headaches, seizures, epilepsy, hemiparesis, developmental delay, and mental retardation. Visual fields may reveal neurologic-related hemianopsia and glaucomatous-type defects. All children seen with port-wine staining should have a complete ocular and neurologic evaluation. The eye exam should be directed at uncovering the presence of choroidal hemangiomas and related glaucoma. Treatment of the glaucoma component of SWS is best achieved with a topical prostaglandin analog, because these medications bypass the very episcleral venous system the vascular anomaly of which causes the elevated intraocular pressure. A neurologic evaluation requires neuroimaging to uncover meningeal angiomas through use of a magnetic resonance imaging (MRI) or computed tomography (CT) scan. Seizures are treated with anticonvulsant drugs such as carbamazepine, phenytoin, and topiramate. Neurosurgical intervention may be necessary in cases of unrelenting seizure activity. Pulsed-dye laser therapy is effective in the amelioration of facial port-wine staining and is often necessary to improve the patient's self-image and confidence.

Nevus

This cutaneous disorder is produced by a proliferation of melanocytes, whereas the common "freckle," or "ephelis," is caused by an enlargement of the melanocytes. The nevus has a definite relationship to sun exposure, particularly in the adult. Melanocytic nevi can be grouped into three general categories: (1) the dysplastic nevus, or atypical mole; (2) the congenital melanocytic nevus, that ranges in size from small to medium to giant (greater than 20 cm in diameter); and (3) the acquired nevus (Table 16-1).

Benign acquired nevi are typically a uniform brown or tan, and have a round shape with sharp, well-delineated borders. Acquired nevi are usually flat, but some noticeable elevation is possible. These benign skin lesions are usually less than 6 mm in

diameter and number from 10 to 40 in the typical adult. Acquired nevi may be present anywhere on the skin and are found most often on sun-exposed areas of the body. The least involved areas are the scalp, breasts, and buttocks. Benign nevi are present in 85% of the world's population.

Dysplastic nevi are atypical moles that are precursors for melanoma (Box 16-4). Dysplastic nevi are transmitted through family members by an autosomal dominant trait involving chromosome 9p16. From one to hundreds of dysplastic nevi may be present on a single individual. Atypical moles have hazy and indistinct borders, and the border pigment may fade off into the surrounding skin. Dysplastic nevi possess variable pigmentation within the lesion, and colors may range from tan, brown, and black to red and pink, all within a single nevus (Figure 16-5). Atypical moles are usually larger than 6 mm in size, and can even reach diameters of 10 mm or more. When dysplastic nevi are present, often more than a hundred are present on a single individual. They are most commonly located on sun-exposed areas of the body, but unlike benign acquired nevi, dysplastic nevi may be present on the scalp, breasts, and buttocks.

Congenital melanocytic nevi are differentiated on the basis of size. The giant congenital melanocytic nevus and small congenital melanocytic nevus are less frequent precursors of melanoma than the dysplastic nevus. Congenital melanocytic nevi are present at birth or shortly after delivery. The giant form can cover half the body, and characteristically have sharp borders and associated hair. The small and medium congenital melanocytic nevi can be slightly raised, are dark brown in color, and have a smooth surface.

TABLE 16-1 CLINICAL CHARACTERISTICS OF NEVI

NEVI	CHARACTERISTICS
Junction nevus	Flat or slightly elevated Uniform pigmentation Smooth surface Regular borders Symmetric shape
Compound nevus	Slightly to moderately elevated Uniform pigmentation Variable surface: smooth, warty, hairy Regular borders Symmetric shape
Dermal nevus	Elevated Uniform pigmentation (lightest colored) Lobular or warty surface Variable stalk with pedunculation Regular borders Symmetric shape

BOX 16-4
CLINICAL CHARACTERISTICS OF DYSPLASTIC NEVI

Simultaneously flat and elevated
Pebbled or "fried egg" surface
Haphazard colors
Regular or irregular borders
Symmetric or asymmetric shape
"Macular tan shoulder"
No hypertrichosis

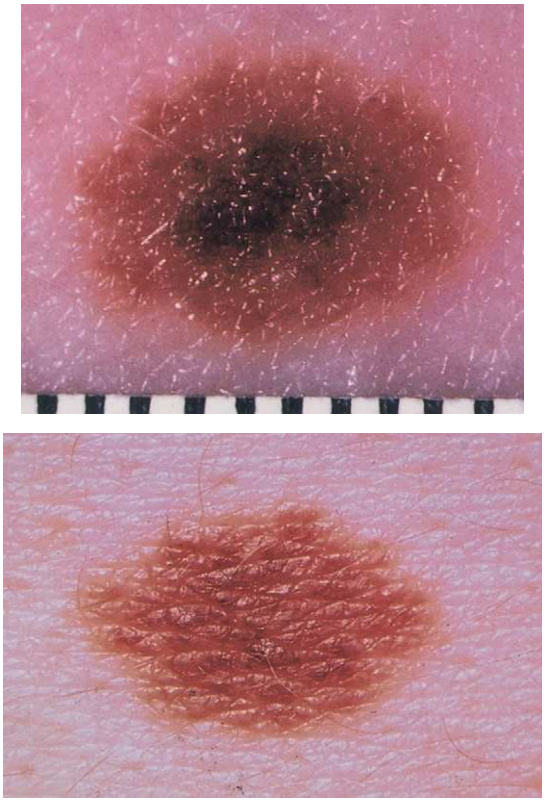

FIGURE 16-5 Dysplastic nevi. (From Goldman L, Ausiello D: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, W.B. Saunders.)

Biopsy of a nevus is necessary in all cases in which detectable growth or changes in shape of the lesion have occurred.

Several other benign nevi can masquerade as melanoma, and both appearance and biopsy are necessary for differentiation. These nevi have been well described by Finberg. Color is a major discriminating characteristic and serves to classify the pigmented lesions that must be distinguished from cutaneous melanoma into two varieties: blue and brown.

The blue nevus is seen as a cerulean blue or gunmetal color. This bluish gray lesion, which does not grow over time and ranges in size from 3 mm to 1 cm, typically occurs on the hands and feet. A dome-shaped, reddish-purple, or blue nodule that blanches from pressure is a hemangioma. The hemangioma is easily confused with a nodular melanoma.

Four brown cutaneous lesions appear similar to cutaneous melanoma: the compound and junctional nevi, and the juvenile and solar lentigines. The round or oval-shaped compound nevus has well-demarcated borders. This dome-shaped lesion ranges in color from flesh-colored to dark brown, and within a single lesion the colors do not tend to vary (Figure 16-6). Another brown lesion is the junctional nevus, which is flat or barely elevated and has sharp borders (Figure 16-7). The junctional nevus differs from the compound nevus in its stippled pigmentary appearance. The dermal nevus is the most elevated of all nevi, and is attached to the underlying dermis by a stalk (Figure 16-8). These nevi often have associated hair and a lobulated appearance. Juvenile and solar lentigines are freckles acquired after birth or from sun exposure. These brown lesions also have sharp borders and measure from 2 mm to larger than 1 cm. The solar lentigo occurs most often on sun exposed areas of the skin. The freckle results from an enlargement of the melanocytes within the basal layer and it has no malignant potential.

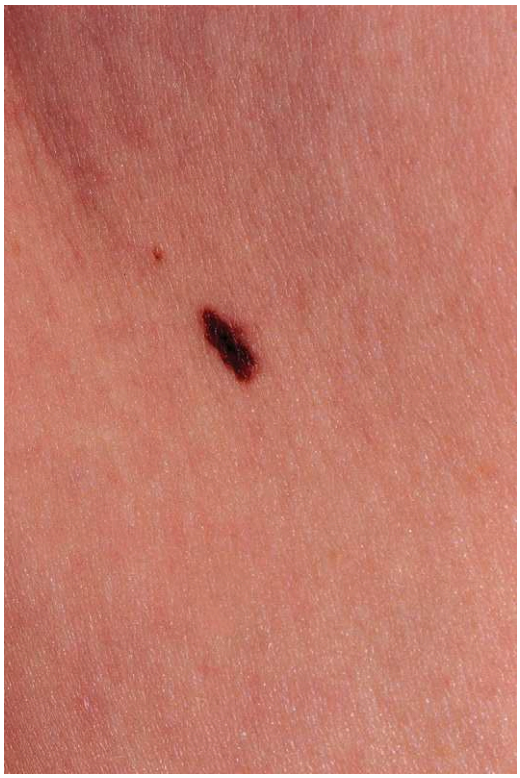

FIGURE 16-7 ■ Junction nevus, with smooth surface, regular borders, and little elevation. (From Bolognia JL, Jorizzo JL, Rapini RP: *Dermatology,* St Louis, 2003, Mosby.)

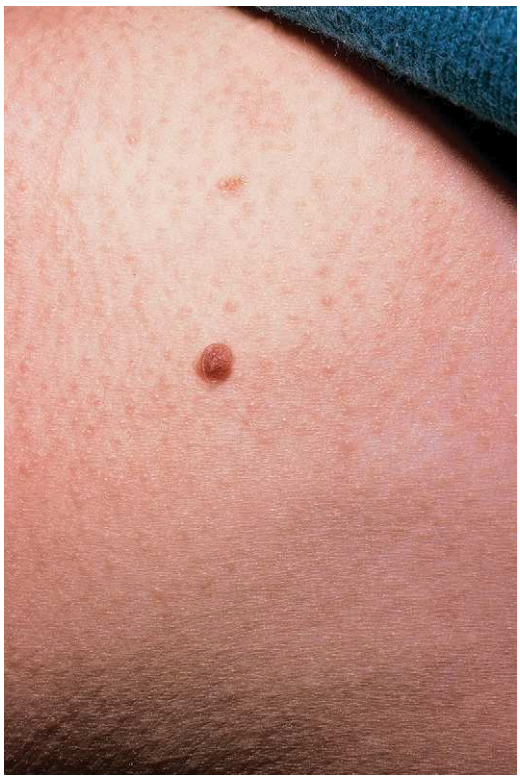

FIGURE 16-6 ■ Compound nevus, with elevated contour, slightly lobulated surface, and regular borders. (From Bolognia JL, Jorizzo JL, Rapini RP: *Dermatology,* St Louis, 2003, Mosby.)

Melanoma

This cutaneous malignancy results from a proliferation of melanocytes. Cutaneous melanomas may be deadly, and must be distinguished from the benign skin lesions listed above. There are several factors that raise the suspicion of malignancy (Box 16-5). More than 45,000 new cases of skin melanoma are diagnosed each year in the United States. Every year more than 7000 people in the United States die of skin melanoma. The tumor occurs at any age and is most common in fair-skinned, blond-haired, blue-eyed individuals with freckles. Melanoma is increasing in prevalence, most likely because of increased sun exposure and a weakening ozone layer in the atmosphere. At present rates, by the year 2010, the lifetime risk of melanoma is expected to be greater than 1% (Table 16-2). According to Finberg, four types of skin melanoma exist, and three of these spread radially first, before becoming deeply invasive. Lentigo maligna melanoma, a brown or tan lesion, occurs most frequently on the sun-exposed surfaces of the cheek and temple in patients who are 70 years or older (Box 16-6). This lesion has a good prognosis and patients are expected to survive 5 to

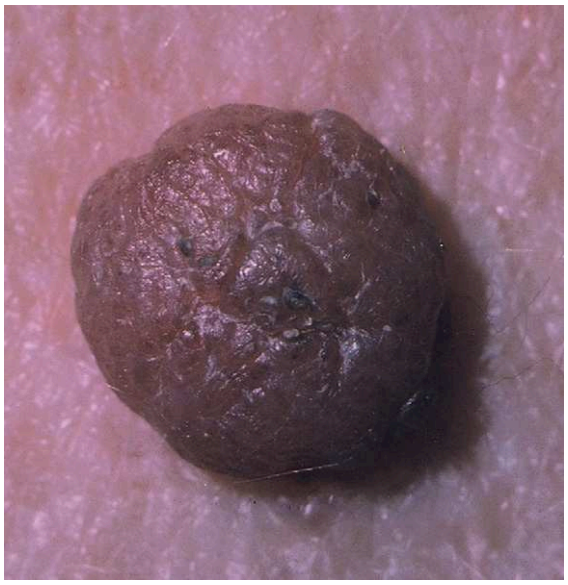

FIGURE 16-8 ■ Dermal nevus, with marked elevation, lobulated surface, and broad attachment (From Goldman L, Ausiello D: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, W.B. Saunders.)

20 years or longer (Figure 16-9). Superficial spreading melanoma, a brown or bluish-red lesion, may have a part that is elevated and occurs at any site in patients typically ages 40 to 50 years (Box 16-7). This lesion has a poorer prognosis, with expected survival of 1 to 7 years (Figure 16-10). *Nodular melanoma* is a reddish-blue mixed with brown lesion occurring at any site in patients aged 40 to 50 years (Box 16-8). These patients have a poor prognosis, with expected survivorship from months to less than 5 years (Figure 16-11). The

TABLE 16-2 RELATIVE RISKS OF MALIGNANT MELANOMA

FACTOR RELATIVE	RISK
Persistently changed or changing mole	Very high
Adulthood	88 ×
Dysplastic nevi	
With history of familial melanoma	148 ×
Without history of familial melanoma	27 ×
Lentigo maligna	10 ×
Large congenital nevi	17 ×
Caucasian race	
Compared with African Americans	12 ×
Compared with Hispanics	7 ×
Previous cutaneous malignant melanoma	5-9 ×
Cutaneous malignant melanoma in parents, children, or siblings of patient with malignant melanoma	2-8 ×
Immunosuppression (renal transplants, lymphoma, leukemia)	4 ×
Skin color	
Patients who tan poorly, burn easily	3 ×
Patients with multiple or severe sunburns	3 ×
Patients with red or blonde hair	2-4 ×
Patients who freckle with sun exposure	2 ×
Sun exposure	
Excessive sun exposure (childhood)	3 ×
Nonmelanoma skin cancer, actinic keratosis	5 ×

Adapted from Rhodes AR, et al: Risk factors for cutaneous melanoma: a practical method of recognizing predisposed individuals, *JAMA* 258:3146, 1987.

BOX 16-5
FACTORS THAT SUGGEST MALIGNANCY

Unpredictable behavior of lesion
Lesion not typical for patient's demographics
Age
Gender
Race
History of dermatologic malignancy elsewhere
History of other malignancy or immunosuppression
Older patients
Excessive ultraviolet exposure
Older patients
Younger patients
Geographic location
Vocation or avocation
Family history of skin cancers
Nonmelanoma skin cancer
Malignant melanoma
Dysplastic nevus syndrome
Fair-skinned patients
Infection, inflammation
Unresponsive to usual therapy
Occurring in a previously stable lesion
Change in a previously stable lesion
Color
Border irregularity
Size and shape
Irregular or unpredictable growth
Other lesion characteristics
Erosion, ulceration, bleeding
Inflammation, infection
Unusually large-sized tumor
Irregular tissue quality, poor surface integrity
Telangiectasias
Concurrent madarosis, conjunctival hyperemia, tearing

BOX 16-6
CHARACTERISTICS OF LENTIGO MALIGNA MELANOMA

Color
- Usually variants of tan or brown
- White, gray-white (regression)
- Reticulated or flecked brown or black
- Variegation of colors

Borders
- Irregular everywhere on lesion
- Extremely convoluted
- Surface characteristics
- Perfectly flat when lentigo maligna
- Largest surface area of melanomas

Signs of invasion
- Irregular surface
- Elevation
- Nodule (brown, black, blue-black)

BOX 16-7
CHARACTERISTICS OF SUPERFICIAL SPREADING MELANOMA

Color variegation
- Tan, brown, dark brown
- Pink, rose, red (inflammation)
- Blue, blue-gray, purple
- White (regression)
- Haphazard arrangement of colors
- Disorganized combinations of brown

Borders
- Circular outline
- Usually irregular
- Increasing irregularity with enlargement
- Margins often elevated, palpable

Surface
- Irregularly elevated, palpable
- Possible nodules (pink-gray, dark gray)
- Possible yellow-brown, warty surface

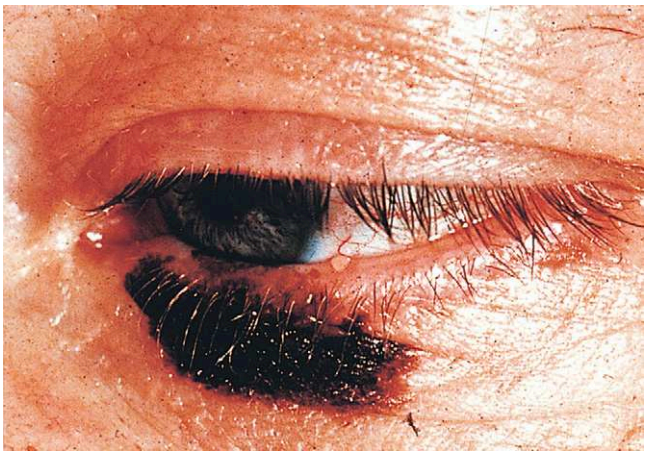

FIGURE 16-9 Lentigo maligna melanoma, with irregular, flat areas of lentigo maligna (Hutchinson's freckle) and nodule with friable surface. (From Yanoff M: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.)

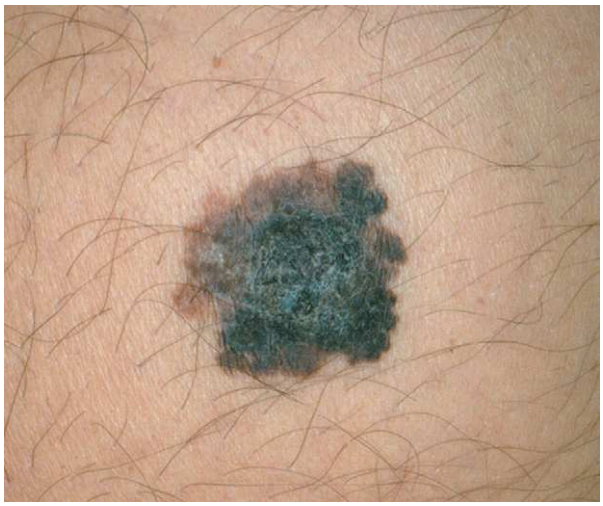

FIGURE 16-10 Superficial spreading malignant melanoma, with regression and nodule development. (From Townsend C, et al: *Sabiston textbook of surgery,* ed 17, Philadelphia, 2004, W.B. Saunders.)

fourth type of melanoma is acral-lentiginous melanoma, which typically occurs on the palms or soles of the feet in patients aged 60 years or older. This melanoma is seen as a flat, dark-brown lesion, but may occur as raised plaques that appear bluish-black. These patients have an expected survival of 1 to 10 years. Patients who observe suspicious moles will note an increase in size or a change in color before the melanoma is ultimately diagnosed. Many cutaneous lesions can be confused for malignant melanoma (Box 16-9). The likelihood of metastases is correlated to thickness of the tumor, with a low-risk tumor having a thickness less than a millimeter. Of patients with melanomas greater than 4 mm in thickness, half of these individuals will develop metastases and die. Tumor satellites typically occur in the dermis or subcutaneous fat near the melanoma. The presence of these satellites tends to indicate spread to the regional lymph nodes. From here the melanomas spread by the lymphatic channels or into the bloodstream. Target organs for spread of melanoma include the liver, bone, lungs, brain, and anterior chamber of the eye. Metastasis of the melanoma has a low cure rate. Prevention of melanoma involves the use of sun block on all individuals in all stages of life. In addition, patients should be educated on the evaluation of atypical moles, and the characteristics that raise suspicion of melanoma. A wide surgi-

BOX 16-8
CHARACTERISTICS OF NODULAR MELANOMA

Color
- Blue-gray
- Purple-blue
- "Thundercloud gray"
- Blue-black
- Reddish-blue
- Rose-gray
- Black
- Pale gray-blue (amelanotic)

Contour
- Spherical
- Polypoid
- Nodule (elevated)
- No flat component to the nodule
- Often symmetrical shape
- Elevated, irregular, blue-black plaque (rare)

Surface
- Smooth
- Ulcerated
- Hyperkeratotic (uncommon)
- Irregular (uncommon)

BOX 16-9
DIFFERENTIAL DIAGNOSIS OF MALIGNANT MELANOMA

- Acquired nevi
  - Junction nevus
  - Compound nevus
  - Dermal nevus
- Blue nevus
- Halo nevus
- Spitz nevus (benign juvenile melanoma)
- Dysplastic nevus
- Lentigo
  - Lentigo simplex
  - Solar lentigo
- Dermatofibroma
- Pigmented seborrheic keratosis
- Pigmented actinic keratosis
- Pigmented basal cell carcinoma
- Merkel cell carcinoma
- Hemangioma
- Hemorrhage into cyst, nevus, or nailbed
- Kaposi's sarcoma
- Ulcerated pyogenic granuloma

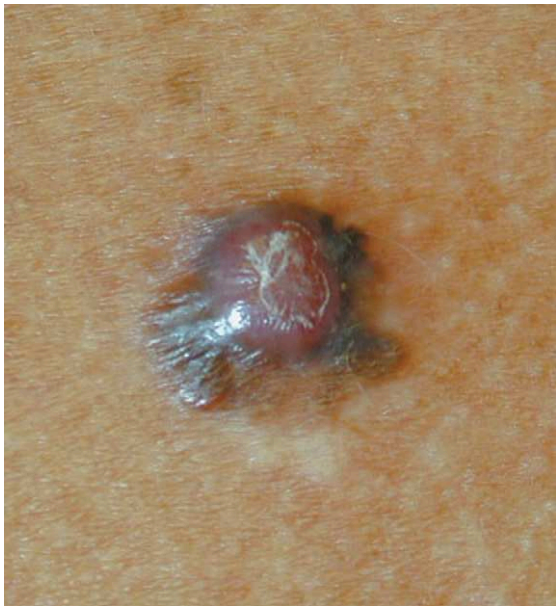

FIGURE 16-11 Nodular melanoma, with surrounding flat component. (From Townsend C, et al: *Sabiston textbook of surgery,* ed 17, Philadelphia, 2004, W.B. Saunders.)

cal excision is necessary to remove all elements of the cutaneous melanoma. Regional node dissection can confirm spread to the lymphatic system, and surgical excision of the nodal micrometastases may reduce the risk of spread and improve survival. In patients with nodal spread of their melanoma, high-dose interferon has been shown to be effective in some cases after surgical excision. Metastatic melanoma is considered incurable, with survival limited to less than a year. Metastases to the brain are treated with radiation and glucocorticoids for reduction of symptomology.

SELECTED ELEVATED SKIN LESIONS

Benign Cutaneous Lesions

Atopic Dermatitis

This cutaneous response is an expression of hypersensitivity without known physical contact with an environmental allergen. Atopy is a cutaneous form of allergic response to exogenous substances in genetically susceptible individuals. If both parents have atopic dermatitis (AD), then more than 80% of their children will develop the condition. AD is very common, occurring in 2% of the human population. AD occurs most often in childhood and in patients with a family history of asthma, hay fever, or dermatitis. Of children with AD, 80% ultimately develop asthma or allergic rhinitis later in life. In fact, nearly one fourth of all Norwegian school children have atopic dermatitis. The disease is immunologically characterized by a decrease in T-lymphocyte cellular immunity and an abnormal and elevated immunoglobulin E (IgE) antibody response. The lesions appear anywhere on the skin as patchy scales. In the acute phase crusts, erythema, and fine scaling of the skin with indistinct borders is present. In the chronic stage lichenification, or thickening, of the skin caused by rubbing or scratching is present. The most common complaint among patients with AD is itching. The most common sites of

AD are the neck, hands, and eyes. Patients with ocular atopic dermatitis complain of itching and foreign body sensations of the eyes. Ocular involvement occurs caused by mast cell degranulation and results in blepharitis, bulbar conjunctival injection, papillae formation on the palpebral conjunctiva, atopic keratoconjunctivitis (AKC), and superficial punctuate keratitis. An infraorbital crease of skin forms in this condition known as the Dennie-Morgan fold. Interestingly, a greater frequency of cataract formation occurs in patients with atopic dermatitis. Patients with atopic dermatitis require a dilated fundus examination, because they are at greater risk of retinal detachment. Treatment of the dermatitis requires fluorinated corticosteroids to reduce cutaneous inflammation. Patients should be advised to avoid rubbing the eyelids, because this trauma will facilitate mast cell degranulation. Ice packs on the eyes will reduce the pruritic response. Typically, a cream-based hydrocortisone is applied with dressings to facilitate the action of the steroid. Topical NSAIDs, such as ketorolac tromethamine (Acular), will reduce the ocular itching associated with AD. Oral corticosteroids may be necessary to quell the systemic inflammation associated with AD. Oral antihistamines are effective in reducing bodywide pruritus.

Contact Dermatitis

Contact dermatitis (CD) is a cutaneous response to direct contact with an allergen that elicits an allergic reaction. The reaction typically occurs from 1 to 24 hours after contact with the offending agent. In some cases the response is immediate, with erythema forming within an hour. In other cases, a delay is caused by sensitization. In delayed sensitivity, a reexposure causes an inflammatory response, usually within 2 to 3 days. Thus, two types of CD exist: irritant CD and allergic CD. Irritant CD is typified by an onset within hours of contact and does not require a sensitizing exposure, whereas allergic CD is a delayed-type sensitivity that requires sensitization with the allergen. CD is a hypersensitivity reaction from exposure to airborne antigens, or direct contact with the skin of drugs, chemicals, or any environmental substance (Box 16-10). A partial list of offending substances includes any drugs, contact lens preservatives, concentrated acids or bases, chemicals, minerals, dyes, and cosmetics. The most common cause of allergic contact dermatitis is contact with plants such as poison ivy, poison oak, and poison sumac. Whether the response is immediate or delayed, the first reaction is typically erythema of the skin with associated burning and stinging. The immediate response is wet and edematous skin. In chronic conditions the skin is typically thick, dry, and scaly (Figure 16-12). The skin begins to itch, particularly if the allergic response is delayed. Papules and vesicles may eventually develop.

BOX 16-10
CAUSES OF ALLERGIC CONTACT DERMATITIS

- Nickel-jewelry, scissors, door handles, watch bands, belt buckles
- Chromium compounds-cement, leather gloves, leather shoes, metals, dyes, photographic processes
- Balsam of Peru: perfumes, shampoos, hair products
- Formaldehyde: cosmetics, wash and wear clothing, paper, glue
- Topical anesthetics: sunburn and antiitch preparations
- Paraben mix: cosmetics, topical creams and ointments, topical corticosteroid preparations
- Paraphenylenediamine: hair dyes, PABA sunscreens, sulfonamides
- Rubber: shoes, elastic, adhesive bandages, condoms, surgical gloves
- Acrylic fabrics
- Other chemicals in personal care products: Imidazolidinyl urea (preservative), wool alcohols, formaldehyde, quaternium-15

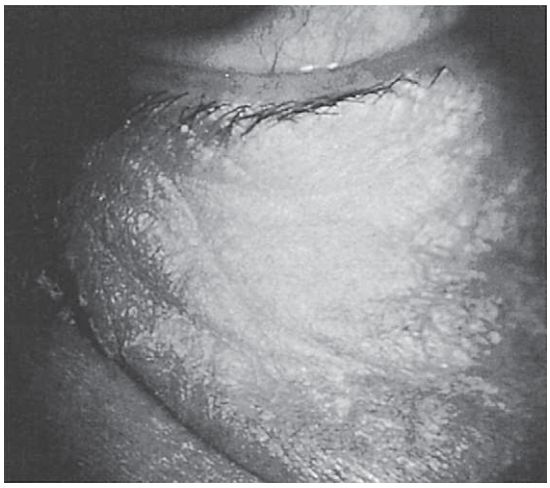

FIGURE 16-12 Contact dermatitis of lower lid caused by dipivefrin ophthalmic solution (Propine): chronic, with dry scaling.

Ocular involvement includes papillary conjunctivitis and serous discharge. Blepharitis with an associated superficial punctate keratitis (SPK) may occur. Treatment of CD includes avoidance of known allergens and application of topical steroid cream to the affected areas. The patient should be encouraged not to scratch the affected areas, because this will worsen the skin condition.

Eczema

Eczema is a chronic dermatitis that is characterized by itching and skin eruptions. For example, chronic hand eczema is a dermatitis produced by exposure to water and detergents. The skin of the hands becomes dry, cracked, and erythematous. The use of rubber gloves

when exposed to water and detergents helps to eliminate this painful form of eczema. Latex allergy may produce an immediate type hypersensitivity reaction, however, that can cause a fatal anaphylactic reaction. Another common eczema condition is asteatotic eczema, or winter itch. During dry, cold, periods of the year, the elderly may complain of superficial itching of the legs. Examination reveals fine cracks, with erythema on the anterior surfaces of the legs. Topical emollients will help alleviate the associated pruritus.

Seborrheic Dermatitis

This form of cutaneous reaction results in dry skin that produces dandruff. The chronic condition is characterized by pinkish-red, greasy scales overlying erythematous plaques. Seborrhea represents a disorder of the sebaceous glands. Although the etiology is unknown, it is believed that *Pityrosporum ovale,* a yeast found around the skin of the glands, has a causative role. Elimination of the yeast tends to improve the condition. Seborrheic dermatitis affects primarily the scalp, where the classic sign is dandruff. The ears, eyebrows, eyelashes, and central face may be involved, however. This condition is characterized by exacerbations and remission, is worsened by stress, and is often found in HIV/AIDS patients and those with Parkinson's disease. The ocular condition associated with seborrheic dermatitis is known as seborrheic blepharitis. Patients complain of an ocular foreign body sensation and burning. Greasy scales, or scurfs, are noted on the skin of the lids. The lids may be erythematous. The hallmark characteristic of seborrheic blepharitis is the production of dandruff flakes of the eyelashes. Treatment of seborrheic blepharitis makes use of lid scrubs with dandruff shampoo and, if resolution is not forthcoming, the application of a topical antibiotic medication. In recalcitrant cases, topical glucocorticoids may be necessary to manage the underlying inflammation.

Psoriasis

This chronic skin condition, which affects as much as 4% of the world's population, causes dry, elevated, and rounded erythematous plaques found most often on the knees or elbows. Characteristically, the plaque is covered in papules and silvery mica-like scales. The most common presenting symptom is pruritus. Psoriasis is worsened by stress, infections, lithium, beta-blockers and antimalarial drugs. It may occur on the eyelids resulting in conjunctivitis and keratitis. An increased frequency of corneal ulcers and iritis is associated with psoriasis of the eyelids. Psoriasis occurs in greater frequency among patients with HLA-B27 related syndromes, and a definite relationship exists between psoriasis and rheumatoid arthritis. Specific agents for the amelioration of psoriasis include retinoid gels (such as tazarotene [Tazorac], a vitamin A analog) used in combination with steroids and ultraviolet light therapy. In addition, methotrexate has been approved for the systemic treatment of psoriatic arthritis. A very effective treatment modality for psoriasis is psoralen ultraviolet A irradiation (PUVA). Topical glucocorticoids may aid in the amelioration of localized plaque-type psoriasis.

Acne Vulgaris

Considered the scourge of the teenage years, acne vulgaris is characterized by small cysts, or comedones, several of which will occur on a patch of erythematous skin. Associated with the comedo are any number of papules, pustules, and nodules. The comedo can be a whitehead or a blackhead. Whiteheads are closed and difficult to express. The content of this papule is typically pus filled with lymphocytes, thus imparting the white color that is accentuated on stretching of the skin. Blackheads have a large follicular opening and are easily expressed. The orifice is filled with dark, oxidized skin oil that imparts the black color. Acne vulgaris is associated with the increase in sebum production from the sebaceous glands that occurs after puberty. The sebum blocks the hair follicle and a comedo forms. Within the comedo, bacteria and yeast act on the sebum to release fatty acids, resulting in inflammation of the cyst wall. Eventually the comedo ruptures, spilling its contents of oil and keratin and leading to an intensified inflammatory response. Early in the evolution of the skin response, acne begins on the forehead. It then tends to travel down the cheeks to the central face. Acne is worsened by physical trauma to the skin and exposure to foreign materials such as chin straps on helmets. This condition may be aggravated by cosmetics and oral steroids. In addition, acne has been associated with use of lithium, isoniazid, and phenobarbital. The goals of acne treatment are the elimination of the comedones, a decrease in sebum production, the reduction of bacteria and yeast populations, and a decrease in overall skin inflammation. Topical retinoic acid prevents formation of comedones and aids in resolution of existing cysts. Topical antibiotics reduce the bacterial population within the comedones. Oral antibiotics reduce bacterial colonization. The synthetic retinoid isotretinoin causes dry skin and cannot be used in pregnancy, but is useful in the treatment of severe nodulocystic acne.

Acne Rosacea

This cutaneous inflammation of the central face, now referred to as rosacea, occurs primarily in adults older than 30 years. Although this condition is seen mostly in women, men are more severely affected. The inflamed skin is characterized by a flushing of the skin across the bridge of the nose and symmetrically involving both

cheeks. The skin is erythematous and contains small telangiectasias and pustules. No comedones are present as in acne vulgaris. Rosacea is caused by a disorder of the sebaceous glands of the skin initiated by bacteria that cause the release of inflammatory stimulating fatty acids. In chronic cases the skin of the nose thickens, enlarging the entire nose. The patients at greatest risk for acne rosacea are those who tend towards easy facial flushing. Patients who report that their faces flush in response to heat, spicy foods, emotions, and alcohol are all at greater risk for acne rosacea. The flush eventually becomes a permanent cutaneous fixture, and the sebaceous glands of the eyelids become involved. The presence of bacteria in the glands causes a release of irritating fatty acids, and these compounds appear to modify the meibomian gland release of lipids into the tears. This alteration in meibomian gland secretory compounds seems to increase surface evaporation from the tear layer, producing dry eye. Rosacea is associated with a litany of ocular complications, including blepharitis, keratitis, and iritis. Chronic rosacea may result in dry eye caused by heightened tear evaporation. The ocular manifestations of chronic dry eye then may yield recurrent hordeola and corneal damage. The treatment of rosacea is best achieved with oral tetracycline in doses of 250 to 1000 mg/d. The antibiotic reduces the free fatty acids released by the surface sebum, and this reduces inflammation and irritation. It is important to note that tetracycline reduces the lipase activity of the bacteria without reducing the bacterial population. Topical low-dose steroids may also be effective in alleviating the erythema, however, fluorinated topical glucocorticoids may actually worsen the condition. Chronic flushing is treated by clonidine, the only drug approved for this purpose.

Stevens-Johnson Syndrome

Also referred to as erythema multiforme major, SJS is characterized by a diffuse erythematous eruption of papules, most often on the soles of the feet and palms of the hand. Small blisters form on deep purple macules. The classic skin lesion of SJS is a bull's-eye or target rash typified by an erythematous ring that surrounds a ring of normal tissue, all encompassing an erythematous center. The skin outbreak coincides with a fever, sore throat, malaise, and myalgias in approximately one third of cases. SJS is a systemic and potentially fatal condition that ultimately involves the mucus membranes of the nose, mouth, and eyes. SJS is a deranged and exaggerated response, usually to medication, and erythema multiforme is typically a reaction to infection. Ocular involvement begins with a pseudomembranous conjunctivitis with bullae formation. Rupture of the bulla leads to conjunctival scarring and symblepharon. The lids may undergo entropion with resultant trichiasis and corneal scarring. Treatment involves removal of the causal agent. In addition, the use of systemic steroids and immunosuppressive agents, while controversial, has been shown to be effective. Topical aminoglycosides reduce the risk of ocular infection, and topical steroids will reduce the ocular inflammation. The fornices should be swept with a glass rod to prevent symblepharon formation between conjunctival surfaces.

Warts

These cutaneous neoplasms are caused by human papillomavirus (HPV) 6 or 12. Also known as verruca vulgaris, or papillomata, these skin lesions are pedunculated, grape-like, and dome-shaped and measure approximately 1 cm in diameter (Table 16-3). The wart has a central core of keratinized debris surrounded by a thick layer of keratin (Figure 16-13). Flat warts, or verruca plana, appear commonly on the face, are flesh-colored or pink, and 1 to 3 mm in size (Figure 16-14). The lesions may affect the genital tract and begin as small papillomas that grow into large, fungus-like lesions. They affect the labia in women and the shaft of the penis in men. Warts can occur on the eyelid margin, and may pour viral particles into the eye, initiating a viral conjunctivitis (Figure 16-15). HPV has been shown to be responsible for uterine cervical cancer. In the spring of 2006, the first HPV vaccination was approved to prevent cervical cancer. Several treatment modalities exist to remove warts depending on location. Cryotherapy with liquid nitrogen is convenient and effective in many cases. Genital warts are treated with podophyllin preparations or topical imiquimod. Trichloracetic acid or cantharidin are topical agents that are also used for wart removal.

TABLE 16-3 CLINICAL CHARACTERISTICS OF VERRUCAE

WARTS	CHARACTERISTICS
Common wart (verruca vulgaris)	Smooth papule (early) Closely lobulated surface (later) Scaly surface, hyperkeratosis Black dots Most likely to appear on hands
Filiform wart	Variably thick base Finger-like Multiple, loosely fused projections Located near mouth, eyes, nose
Flat wart (verruca plana)	Flat-topped Smooth papule Flesh-colored or pink Minimal or no scale Located on forehead, beard area, hands

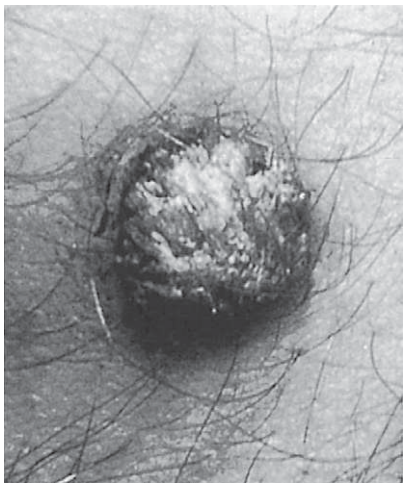

FIGURE 16-13 ■ Common wart (verruca vulgaris), with heavily keratinized, lobulated surface.

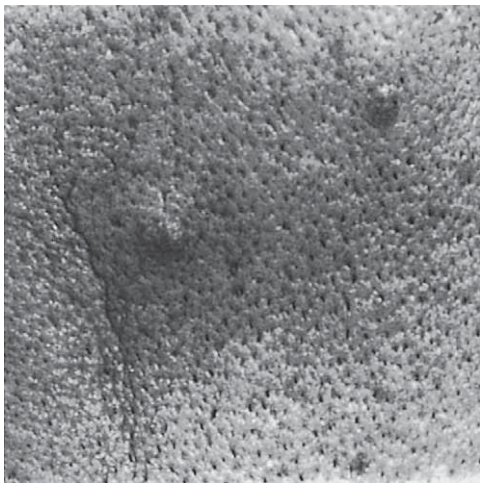

FIGURE 16-14 ■ Two flat warts (verruca plana) that are slightly elevated, papular, and flesh-colored.

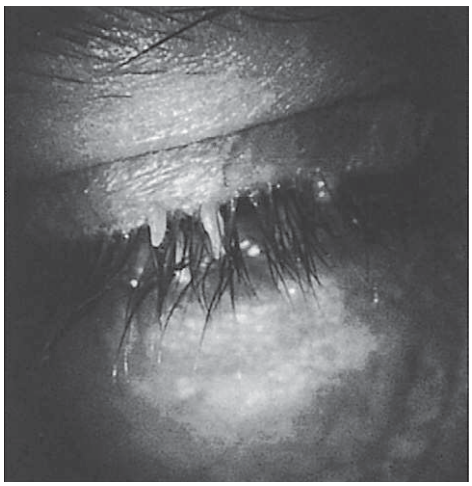

FIGURE 16-15 ■ Multiple filiform warts at the upper lid margin.

Benign Elevated Ocular Skin Tumors

Papilloma

The squamous papilloma is also known as an acrochordon, or skin tag, and appears as a projection of the skin in a frond-like configuration (Table 16-4). This papilloma is the most common of all benign eyelid lesions. Viewed histiologically, this tumor has an increased thickness caused by redundant epithelium (Figure 16-16). These lesions may be excised for cosmetic reasons.

Inclusion Cyst

These slow-growing epidermal lesions are the second most common benign lid lesion, and they can occur spontaneously or from trauma. The inclusion cyst arises from the infundibulum of hair follicle, appearing as a firm nodule on the skin surface (Table 16-5). As a cyst, it is filled with keratin, and several forms of inclusion cyst exist (Figures 16-17 and 16-18). Removal is best achieved through excision or curettage.

Sudoriferous Cyst

Caused by occlusion of the gland of Moll duct, these cysts are associated with the eyelash follicle. The cyst appears filled with translucent fluid (Table 16-6). The syringoma are a common and benign variation of the

TABLE 16-4 CLINICAL CHARACTERISTICS OF PAPILLOMAS

PAPILLOMA	CHARACTERISTICS
Skin tag	Flesh-colored or brown Variably thick stalk Sessile or pedunculated Lobulated surface (cauliflower-like)
Polyp	Flesh-colored or brown Narrow stalk Pedunculated Broad tip

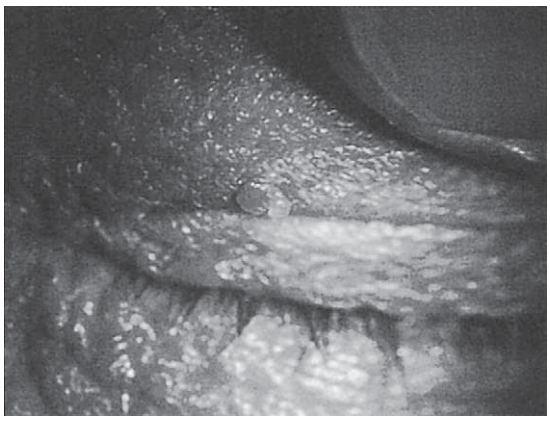

FIGURE 16-16 ■ Skin tag on upper lid: flesh-colored, sessile.

TABLE 16-5 CLINICAL CHARACTERISTICS OF INCLUSION CYSTS

CYSTS	CHARACTERISTICS
Milia	Small (1 mm) Elevated Flesh-colored, yellow, or white
Epidermal cyst	Central orifice or channel Firm, rubbery Yellow Keratin debris
Sebaceous cyst	Firm, rubbery Yellow Glands of Zeis, eyebrows
Senile sebaceous hyperplasia	Yellow or flesh-colored Elevated papules Umbilicated Doughnut-shaped

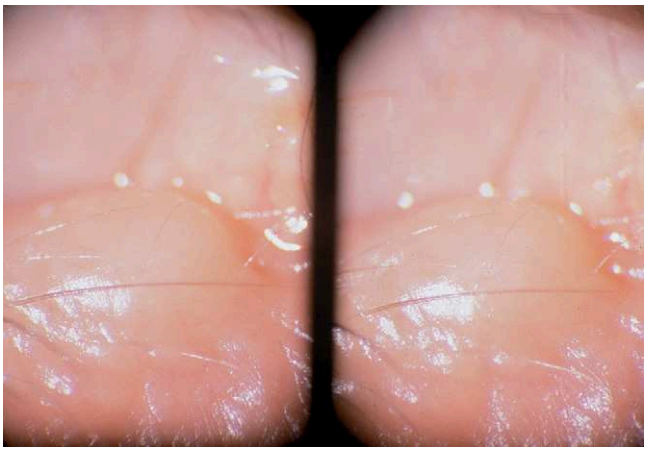

FIGURE 16-17 Epidermal cyst on upper eyelid, with fine texture and small, central drainage channel.

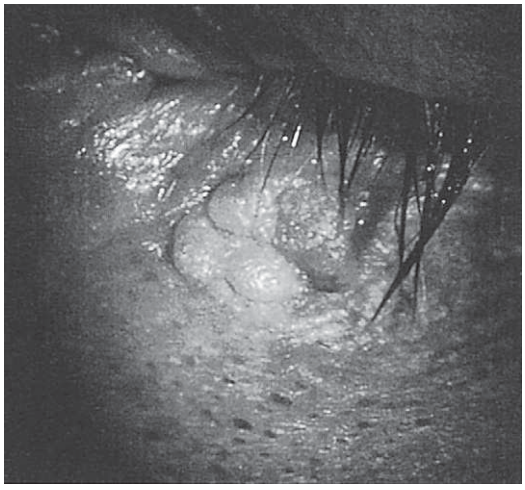

FIGURE 16-18 Senile sebaceous hyperplasia, with multiple, lobulated papules.

TABLE 16-6 CLINICAL CHARACTERISTICS OF SUDORIFEROUS CYSTS

CYSTS	CHARACTERISTICS
Sudoriferous cyst	Tense Fluid-filled Translucent Glands of Moll
Syringoma	Flesh-colored Papules Lower lids Females (teens, 20s)

sudoriferous cyst, that appear as waxy, pale, and yellowish papules near the eyelid margin (Figure 16-19). These cysts are common in pregnant women.

Seborrheic Keratosis

This benign skin condition of the elderly is a growth of the basal epithelial cells and contains pseudocysts. The classic appearance is that of a greasy, oily, pigmented lesion that is "stuck on" to the underlying epidermis (Box 16-11). The surface of the lesion is crust-like (Figure 16-20), and can be removed by excision for cosmetic considerations. Constant irritation of the seborrheic keratosis may result in a cutaneous horn.

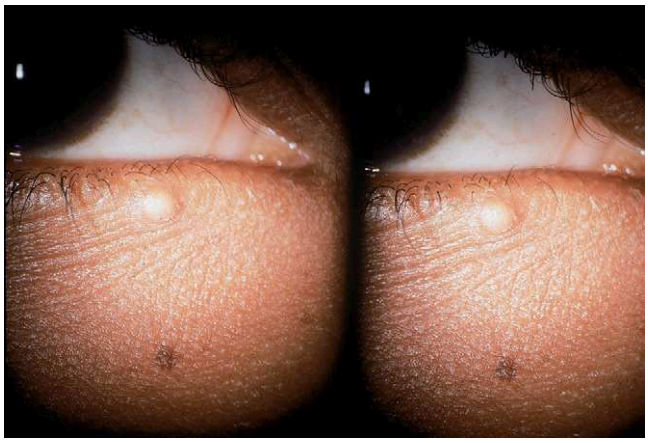

FIGURE 16-19 Sudoriferous cyst at inner canthus; fluid-filled, translucent, with level of cellular debris.

BOX 16-11
CLINICAL CHARACTERISTICS OF SEBORRHEIC KERATOSIS

Variable tan to black color
Multiple confluent papules
Granular, keratinized, crumbling surface
Possibly multilobed or wart-like
Variable elevation (flat to pedunculated)
"Stuck on"
Sharp borders

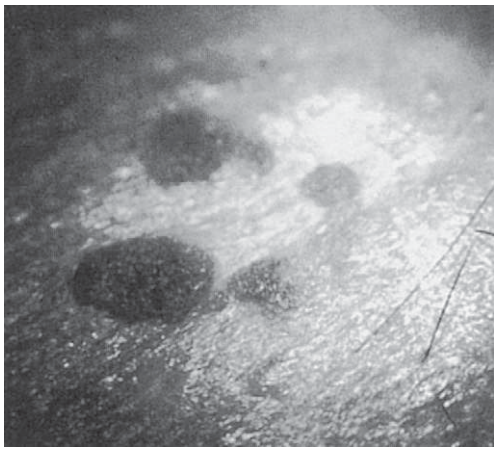

FIGURE 16-20 ■ Multiple seborrheic keratoses, with granular, crumbling keratinized surfaces.

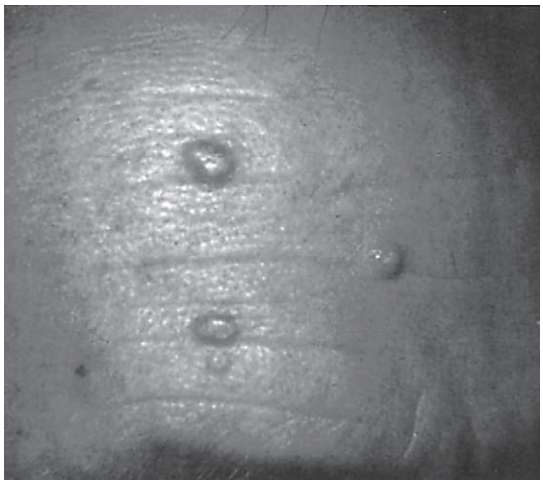

FIGURE 16-22 ■ Multiple molluscum contagiosum lesions, several with central umbilication.

Cutaneous Horn

Also known as inverted follicular keratosis, the appearance of the cutaneous horn is similar to a wart (Box 16-12). Histiologically, lobules of proliferating basal and squamous cells are present (Figure 16-21). Complete excision is used for cosmetic reasons.

Molluscum Contagiosum

These are waxy, nodular lesions similar to warts with umbilicated central ulcers (Figure 16-22). If located on the eyelid, an associated follicular conjunctivitis may be present. Many of these lesions spontaneously resolve in less than a year, thus a period of observation and photography is recommended. Removal is by excision, curettage, or cryotherapy.

BOX 16-12
CLINICAL CHARACTERISTICS OF CUTANEOUS HORN

Keratin build-up
Possibly conical shape
Associated with a primary lesion

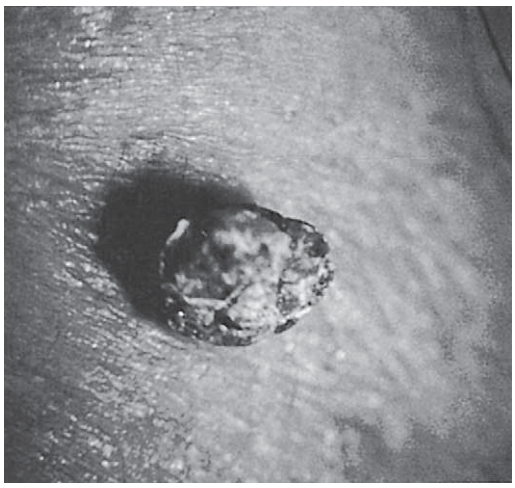

FIGURE 16-21 ■ Cutaneous horn developing on verruca vulgaris.

Premalignant Epithelial Lesions

Keratoacanthoma

This premalignant epithelial lesion grows quickly and has an ulcerated center filled with keratin (Box 16-13). Keratoacanthoma appear most often on sun-exposed areas of the body (Figure 16-23). Complete excision of the lesion is recommended, because these are considered low-grade squamous cell carcinomas.

Actinic Keratosis

Actinic keratosis is a premalignant epithelial lesion that appears as a flat, erythematous, scaly lesion (Box 16-14). These lesions occur most often on sun-exposed areas of the body (Figure 16-24). More than one tenth of these lesions transform into squamous cell carcinoma, thus rapid identification and excision is necessary in all cases.

Malignant Cutaneous Lesions

Basal Cell Carcinoma

This nonmelanoma skin malignancy arises from the epidermal basal cells, and there are several types of basal cell carcinomas each with their own inherent characteristics (Table 16-7). The classic appearance of the BCC is an elevated, pearly nodule with an umbilicated bleeding center (Figure 16-25). These lesions can present with a variable amount of pigment, and each type of BCC can be confused with a wide variety of other skin conditions (Box 16-15). BCC grows fairly slowly, and the tumor rarely

BOX 16-13
CLINICAL CHARACTERISTICS OF KERATOACANTHOMA

Single lesion
Dome-shaped
Pink or red papule
Central crater or umbilication
Keratin cap
Less common: elevated, warty, ulcerated

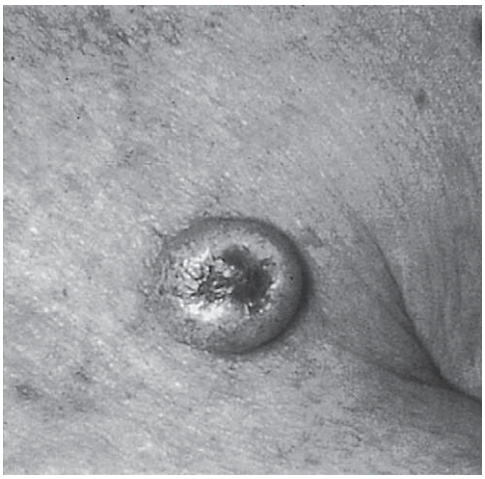

FIGURE 16-23 ■ Keratoacanthoma, typically presenting as a dome-shaped papule with a central keratin core.

BOX 16-14
CLINICAL CHARACTERISTICS OF ACTINIC KERATOSIS

Initially flat
Pink, increased vascularity
Increasing erythema over time
Increasing surface keratin over time

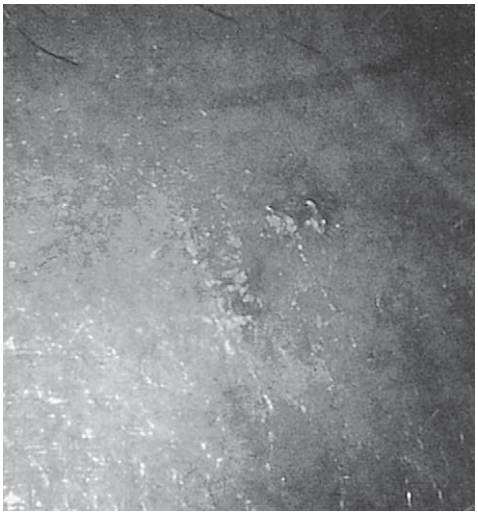

FIGURE 16-24 ■ Early actinic keratosis, slightly elevated, with roughened surface but without erythema.

TABLE 16-7 CLINICAL CHARACTERISTICS OF BASAL CELL CARCINOMA

BASAL CELL CARCINOMA	CHARACTERISTICS
Nodular	Smooth nodule
	Variable colors
	Superficial telangiectasias
	Possibly pearly surface
Noduloulcerative	Nodule
	Central umbilication, ulceration
	Pearly border
	Serosanguineous crust
Sclerosing	Scar tissue
	Hard, pale, waxy, "old ivory"
	Prominent telangiectasias
	No pearly borders
Multicentric	Nodules
	Variable color
	Possible telangiectasias
	"Normal skin"
Superficial	Erythematous
	Scaly, eczematoid
Pigmented	Nodular
	Superficial telangiectasias
	Pearly border
	Dark color (brown or blue-black)
Cystic	Translucent nodule
	Resembles epidermal cyst

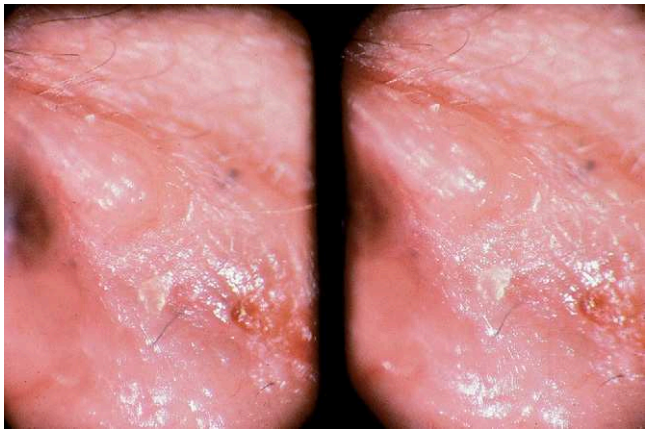

FIGURE 16-25 ■ Noduloulcerative basal cell carcinoma, with pronounced erosion and scabbing.

metastasizes. Nonetheless, it is the most common eyelid malignancy and accounts for more than 90% of all malignant eyelid tumors. BCC is most common in fair skinned, blond, blue-eyed individuals descended from Scandinavia or Scotland. If the canthus is involved, a 3% mortality rate is associated with this tumor. The growth begins as a minute telangiectatic spot, typically on the eyelid, lid margin, or

BOX 16-15
CONDITIONS FREQUENTLY CONFUSED WITH SEBACEOUS GLAND CARCINOMA

Chalazion
Basal cell carcinoma
Squamous cell carcinoma
Unilateral blepharitis
Unilateral blepharoconjunctivitis
Granulomatous lid lesions (from tuberculosis, sarcoid, syphilis)
Meibomitis
Superior limbic keratoconjunctivitis
Leukoplakia
Ocular pemphigoid
Carcinoma in situ
Cutaneous horn
Lacrimal gland tumor

bridge of the nose (Figure 16-26). Biopsy of these small red lesions usually confirms the presence of basal cell carcinoma even before the classic signs of bleeding or the presence of a pearly-white margin appears (Figure 16-27). Treatment of BCC is usually directed at full-thickness dissection. Most often, dermatologists use electrodissection and curettage for low-risk tumors, and more aggressive tumors are excised. Mohs micrographic surgery is used for BCC of the eyelids, because it permits maximal histiological control with minimal tissue disruption.

Squamous Cell Carcinoma

Much less common than BCC but much more deadly, squamous cell carcinoma (SCC) appears as a greasy, reddened, ulcerated nodule or superficial erosional lesion (Figure 16-28) that disrupts the normal anatomy

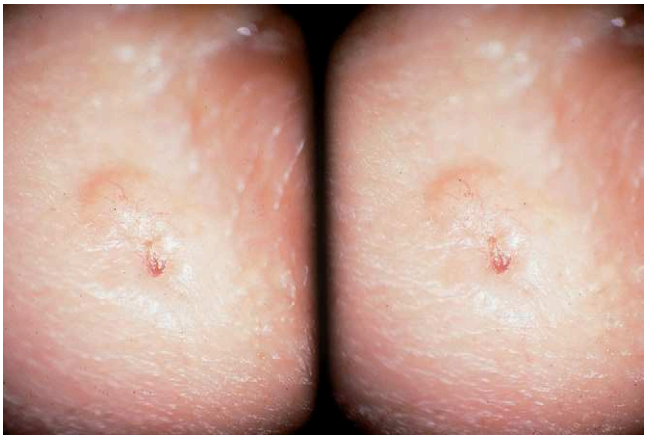

FIGURE 16-26 Sclerosing basal cell carcinoma, with appearance of scar tissue, lacking erosion or crusting.

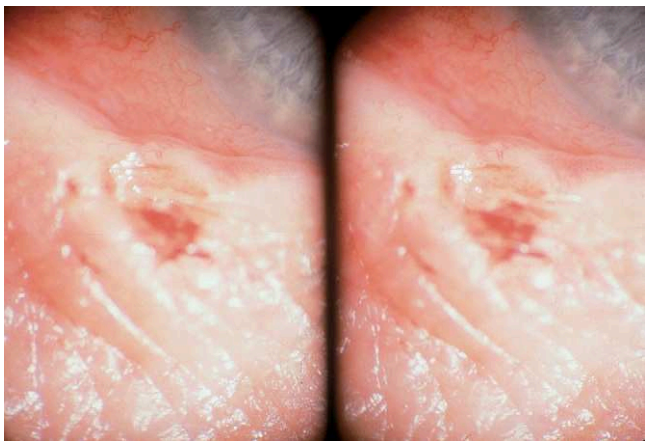

FIGURE 16-28 Nodular basal cell carcinoma on lower lid, flesh-colored, with slight central umbilication but no erosion.

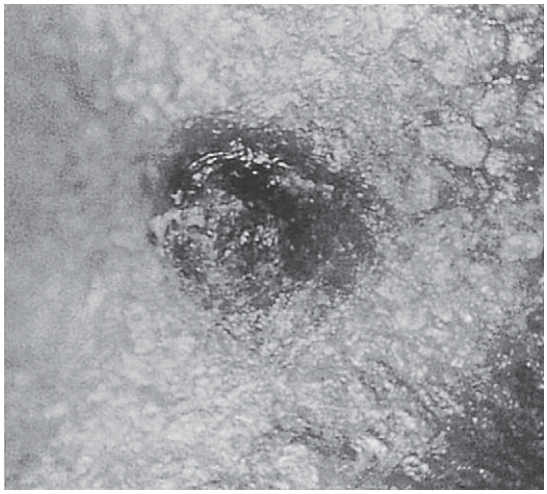

FIGURE 16-27 Early squamous cell carcinoma, with erythema and elevated scale.

BOX 16-16
CLINICAL CHARACTERISTICS OF SQUAMOUS CELL CARCINOMA

Firm nodule
Flat patch
Erythematous
Variable surface scale
  Heavy, thick when derived from actinic keratosis
  Mild when derived from actinically damaged skin
Fissured surface
Ulceration
Bleeding, crusting
Purulent discharge, infection
Wartlike
Cystic
Cutaneous horn
No telangiectasias
No pearly borders

BOX 16-17
CONDITIONS CONFUSED WITH SQUAMOUS CELL CARCINOMA

Actinic keratosis
Adenoacanthoma
Adnexal carcinoma
Basal cell carcinoma (nodular)
Basal cell carcinoma (noduloulcerative)
Basal cell carcinoma (morpheaform)
Basal cell carcinoma with pseudoepitheliomatous hyperplasia
"Benign keratosis" (seborrheic keratosis)
Bowen's disease
Cutaneous horn
Inverted follicular keratosis
Keratoacanthoma
Papilloma
Pseudoepitheliomatous hyperplasia
Sebaceous gland carcinoma
Seborrheic keratosis with surface irritation
Wart (verruca)

of the skin, lower lip, or eyelid margin (Box 16-16). SCC arises from keratinized epidermal cells and can be confused with a host of other cutaneous lesions (Box 16-17). Overlying telangiectasias are an uncommon feature of SCC. SCC is very aggressive, and disseminates quickly throughout the body through the nerve endings, lymph channels, and bloodstream. Surgical excision and radiation treatments are the standard treatment modalities. Metastases are treated with lymph node dissection and radiation.

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CHAPTER 17

Neurology*

CHAPTER OUTLINE

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NEUROLOGIC INVESTIGATIONS

When formulating a neurologic investigation in a particular case, the examiner must take into account the clinical context and the differential diagnosis. In this way, the investigation confirms a likely diagnosis and excludes other possibilities. In most neurologic cases, a differential diagnosis is developed headed by the most likely diagnosis. The examiner must remain unbiased during investigations, however, because it is all too easy to interpret the data to fit a presumed diagnosis. Neurologic investigations should therefore be as free of prejudice as possible. There are two forms of neurologic investigation; anatomical and physiological studies. Anatomical studies make use of neuroimaging techniques and are useful in assessing the physical damage wrought by a clinical entity. Physiologic studies evaluate the functional effects of a neurologic disorder. The anatomical and physiological results are then correlated and interpreted in the context of the medical and physical examination. Prognostic and therapeutic strategies can be formulated and modified based on the results of the neurologic investigation.

Electrophysiology

This branch of diagnostic testing makes use of the recorded electrical activity of the brain, nerves, and muscles. Abnormal results are correlated to other findings and interpreted in the context in which they were obtained.

Electroencephalography

Electroencephalography (EEG) records the electrical activity of the brain by electrodes placed on the scalp. This study is noninvasive, easy to perform, inexpensive, and is useful in the diagnosis and prognosis of several disorders.

Epilepsy

EEGs are most useful to diagnose epilepsy. Patients who experience repeated epileptic seizures often have modified EEG readings, because abnormal electroform spike discharges are present. Epileptics with normal EEGs have a much more favorable prognosis than those with abnormal background activity. Furthermore, EEG is helpful in classifying the seizure disorder and thus aids in the selection of anticonvulsant medication. In fact, EEG can be used to monitor the effectiveness of the antiseizure medication.

Structural Brain Lesions

Although brain tumors may be detected on EEG readings, this study is an indirect and therefore somewhat imprecise technique. Focal structural abnormalities produce focal slow-wave disturbance or a loss of EEG activity. Newer neuroimaging techniques have made the use of EEG in this context obsolete.

Establishment of Death

Cortical death is implied by the establishment of electrocerebral silence. In fact, as consciousness is depressed the EEG becomes slower, and this is manifested in cases of drug use and hypothermia. By use of EEG, consciousness may be established as present in patients who are comatose.

Evoked Potentials

In the evoked potentials (EPs) technique, noninvasive stimulation is used to monitor the integrity of neurologic pathways. Evoked potentials are useful in the detection and monitoring of multiple sclerosis, Lyme disease, AIDS, neurosyphilis, and some vitamin deficiencies. EPs are monitored during neurosurgery to test the integrity of neural structures during operative procedures. Several types of evoked potentials are measured, including visual, auditory, and somatosensory.

Visual Evoked Potentials

In this technique, a checkerboard pattern is used to elicit visual evoked potentials (VEPs) from one eye and recordings are made from electrodes placed on the scalp.

Auditory Evoked Potentials

Repetitive clicks to one ear are used to elicit auditory evoked potentials (AEPs).

Somatosensory Evoked Potentials

In somatosensory evoked potentials (SEP), responses to the electrical stimulation of a peripheral nerve are measured from the scalp and spine.

Electromyography

Electromyography (EMG) measures the electrical activity in a certain section of a muscle through an inserted needle electrode. The pattern of the electrical activity given off by the muscle is evaluated during rest and physical exertion. EMG can detect abnormalities of the motor units (nerve, muscle, and neuromuscular junction) and determine the site of the lesion. EMG can also detect neuromuscular disease in its earliest stages and before any abnormalities are appreciated clinically. EMG cannot determine an etiology, but it is an effective technique in establishing the presence of a neuromuscular abnormality and determining the site of involvement.

Cranial Imaging

X-Ray

The x-ray, or plain films, can visualize abnormalities of the bones of the skull (Figure 17-1, *A* and *B*). X-ray is effective in detecting bone fractures, foreign bodies,

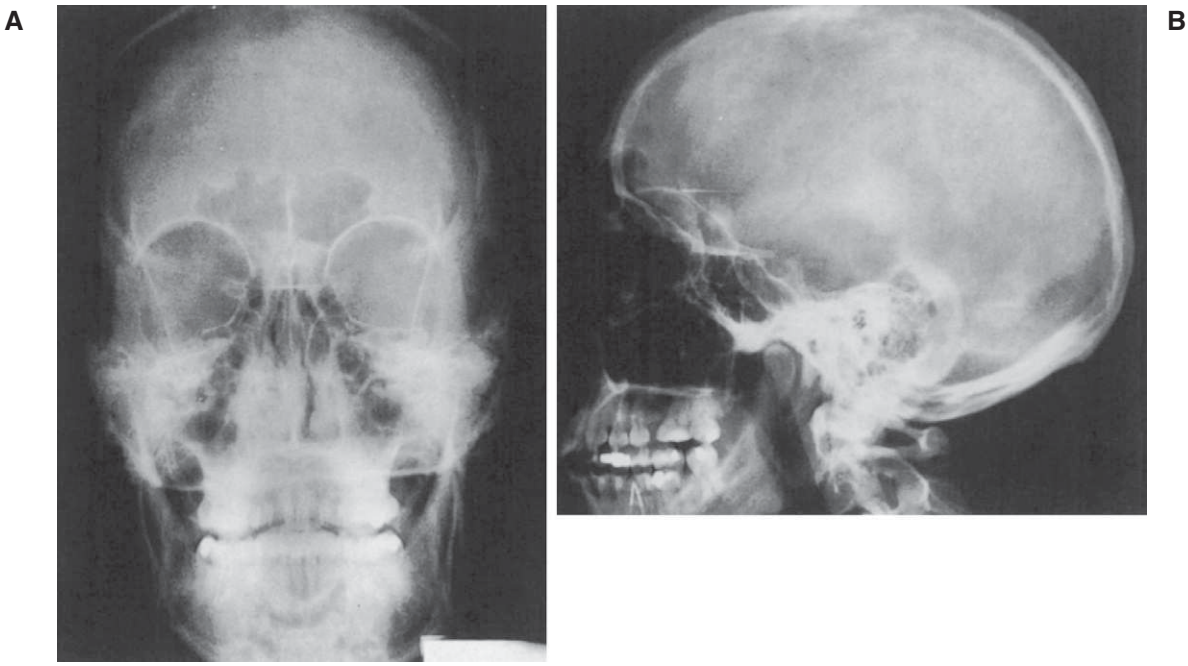


FIGURE 17-1 ■ Cranial roentgenograms, in anteroposterior **(A)** and lateral **(B)** projections. (Courtesy Barry B. Goldberg, M.D., and Daniel A. Merton, B.S.; R.D.M.S., Department of Radiology, Jefferson Medical College, Philadelphia, Pa.)

and intracranial calcification. The sella turcica can be studied during time to evaluate changes in size. Plain films are rarely used to study the skull since the advent of CT scanning.

Computed Tomography Scan

A form of noninvasive neuroimaging, computed tomography (CT) makes use of x-ray photography of the brain or spinal cord to produce a series of photographic slices through the tissues. A computer is used to guide the photography and assemble the images. CT allows for a sequential "slicing" of the involved area of interest and a determination of the size and location of a neurologic lesion (Figure 17-2). This method may be combined with an intravenous contrast agent to better detect lesions. CT is excellent in detection of focal neurologic lesions and brain tumors, evaluation of brain tissues after stroke or trauma, and the detection of cerebral infarct. In addition, CT scanning can detect blood in the brain caused by a subarachnoid hemorrhage. In cases of cerebral infarct, it may take several hours for a CT scan to reveal tissue damage. In most cases, however, CT scan without contrast is used in cases of acute stroke to determine whether the etiology was occlusion or hemorrhage. Because CT requires less time, it is superior to MRI in evaluating head trauma, intracranial hemorrhage, and bone injury. In addition, CT is superior to MRI in revealing spinal bone fractures. In follow-up, MRI is more useful for these conditions than CT scanning.

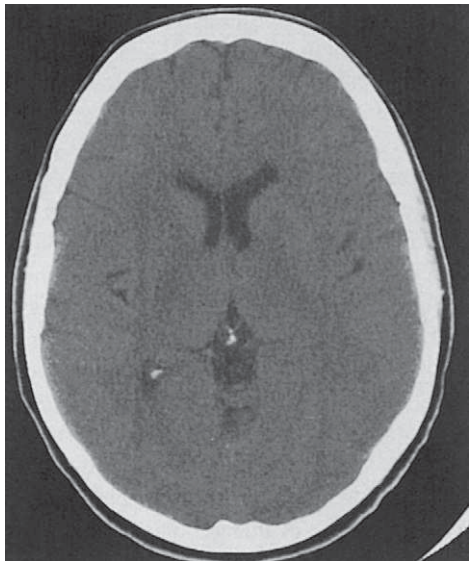


FIGURE 17-2 ■ Computed tomography scan of the brain of a normal subject in axial projection. (Courtesy Barry B. Goldberg, M.D., and Daniel A. Merton. B.S., R.D.M.S., Department of Radiology, Jefferson Medical College, Philadelphia, Pa.)

Magnetic Resonance Imaging

In magnetic resonance imaging (MRI), no radiation is used. Instead, a magnet is used to align protons in the tissues of the patient. A radio frequency is used to stimulate these aligned protons to vibrate. The echo of the vibration is detected by sensors and a computer maps the location and intensity of these signals. The MRI can be

pulsed to detect subtle differences in tissue density that cannot be achieved by CT scanning. For example, the MRI can detect the difference between white and gray matter in the brain (Figure 17-3). MRI can detect, by T2-weighted imaging, cerebral infarcts just hours after vascular occlusion. MRI does not image cerebral hemorrhaging well within the first 36 hours, and usually the CT scan is used in cases of acute stroke. The MRI cannot define a vascular lesion without use of angiography. MRI is superior to CT scanning when evaluating tumor, and is certainly superior in cases of pituitary lesions. MRI is far superior to CT scan in evaluating the neurologic lesions associated with multiple sclerosis. Likewise, MRI is very sensitive to focal cerebral edema in cases of infection. MRI is contraindicated in patients with ocular metallic foreign bodies, metallic intracranial clips, pacemakers, and cochlear implants.

Diffusion-Weighted Magnetic Resonance Imaging

This form of MRI is invaluable in the evaluation of stroke, because it can visualize cerebral ischemia within hours of a vascular event. It can permit use of thrombolytic agents early in the course of the condition by effectively discriminating between acute and older infarcts. This form of imaging is based on the microscopic motion of water protons in tissues.

Perfusion-Weighted Magnetic Resonance Imaging

When a contrast medium such as gadolinium is injected, MRI can be used to measure relative blood flow through the vessels of the brain. This technique can detect abnormalities in blood flow, detect early ischemia shortly after occlusion or hemorrhage, and confirm early reperfusion shortly after treatment for ischemia. The technique can be used without contrast by using the patient's own blood as an endogenous source of contrast material.

Positron Emission Tomography Scan

Positron emission tomography (PET) detects functional rather than structural abnormalities of the brain. This method is most useful in the evaluation of surgical candidates with epilepsy, the differential diagnosis of epilepsy, the selection of tumor biopsy sites, and in the

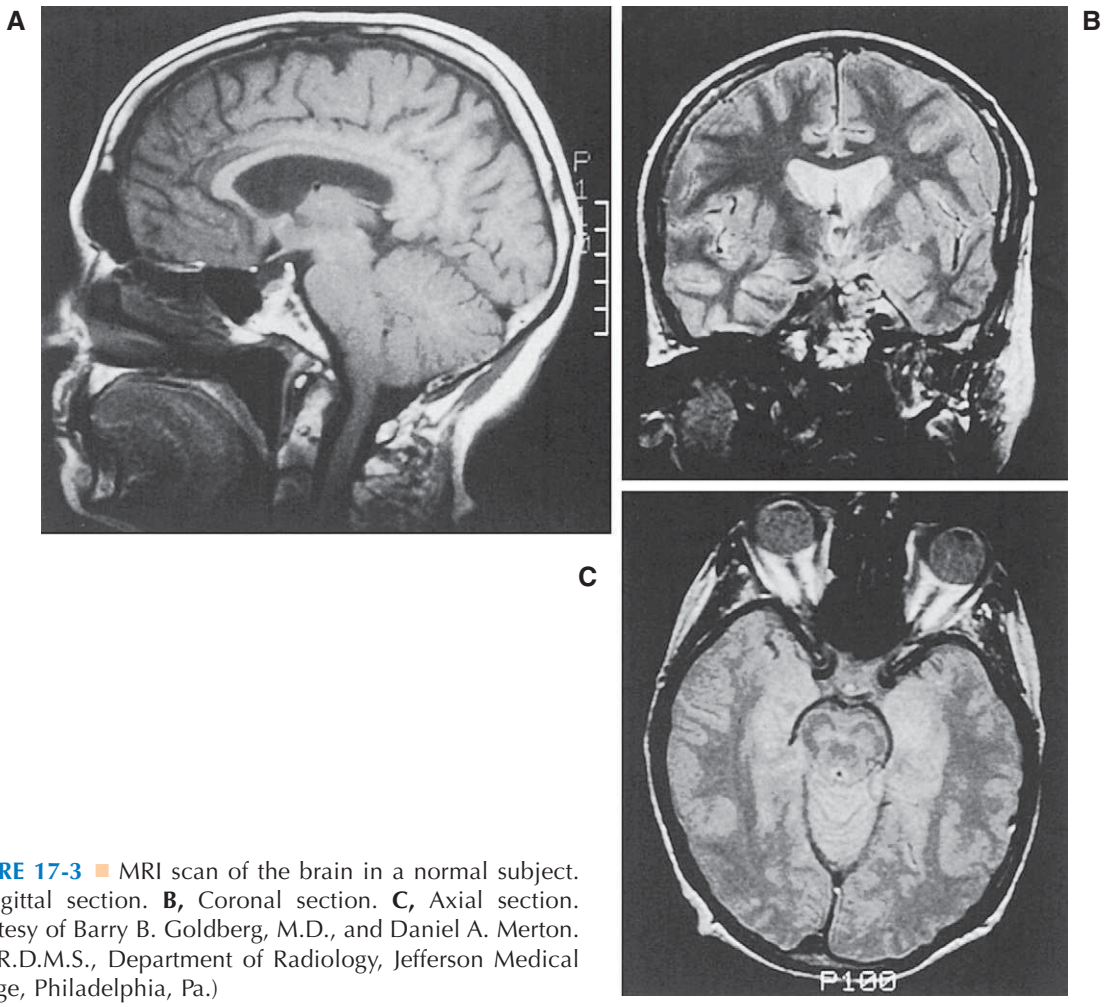


FIGURE 17-3 ■ MRI scan of the brain in a normal subject. **A,** Sagittal section. **B,** Coronal section. **C,** Axial section. (Courtesy of Barry B. Goldberg, M.D., and Daniel A. Merton. B.S., R.D.M.S., Department of Radiology, Jefferson Medical College, Philadelphia, Pa.)

evaluation of Alzheimer's disease. PET scanning exposes the patient to radiation, because it uses positron-emitting radiopharmaceuticals to map the functioning of the brain (Figure 17-4). PET is an expensive study and significant justification is needed to order this scan.

Arteriography

In this technique a contrast dye injected through a catheter is used to image the intracranial circulation. It is useful in the diagnosis of intracranial aneurysm, arteriovenous (AV) malformations, subarachnoid hemorrhage, vascular lesions, vasculitis, and space-occupying lesions. Arteriography is a potentially deadly test, because a 1% mortality rate is associated with the procedure. Patients may be allergic to the contrast material and an enormous amount of radiation is involved in imaging the vessels.

Magnetic Resonance Arteriography

Magnetic resonance arteriography (MRA) reduces the risks inherent in arteriography and is useful in visualizing the carotid arteries. Dissection of the carotid artery is visible in MRA images. MRA is used to screen patients for carotid artery stenosis and is only of value in high velocity vessels. In low-flow vessels, occlusions are difficult to identify. Patients suspected of having an intracranial aneurysm should have conventional arteriography and not MRA.

Computed Tomographic Arteriography

CT arteriography uses an injection of a contrast dye in combination with a CT scanner and is of limited value in carotid stenosis. This method is of value in detecting intracranial aneurysm and conventional arteriography is preferred over this technique. CT arteriography is of most value in acute stroke, in which it can pinpoint the location of the lesion and detect collateral blood flow days after the vascular occlusion.

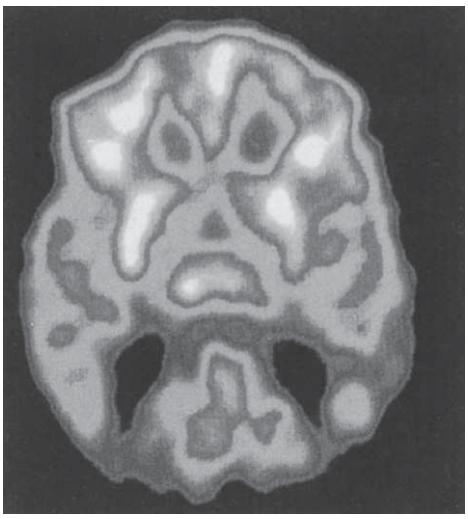


FIGURE 17-4 ■ Positron emission tomography (PET) scan of the brain of a normal subject, recorded following the administration of radioactive fluorodeoxyglucose. The lighter areas are the most active metabolically and the darker areas the least active. (Courtesy of P. David Mozley. M.D., Division of Nuclear Medicine, University of Pennsylvania, Philadelphia, Pa.)

B-Mode Ultrasonography

In this technique sound waves are used to penetrate tissues. The sound reflects off of tissues of various densities, and the echoes are plotted on an oscilloscope screen. Ultrasound is effective in imaging the carotid artery bifurcation in the determination of extracranial vascular disease. The carotid artery wall is visualized and the level of stenosis can be evaluated. A modification of B-mode ultrasonography, Doppler ultrasonography, makes use of sound waves of a specific frequency that are used to bounce off red blood cells, thus achieving a measurement of blood flow velocity. Doppler ultrasonography can detect increases in blood flow velocity that occur because of luminal wall narrowing. Further modification of the ultrasound technique permits evaluation of intracranial arterial lesions through transcranial Doppler ultrasonography. When B-mode is combined with Doppler ultrasonography, the resultant duplex instrument can be particularly effective in evaluating aberrations of blood flow through vascular lesions. Duplex ultrasonography of the carotid artery is an effective screening technique when evaluating candidates for arteriography.

Lumbar Puncture

This technique procures samples of the intracranial fluid (ICF) for testing and evaluation. Lumbar puncture is useful in cases of meningitis, intracranial hemorrhage, and abnormalities of the intracranial pressure (ICP). It should not be performed in the presence of a brain tumor (a drop in ICP can cause a herniation), or if a coagulopathy is present. The procedure is performed with the patient lying on his or her side, facing away from the examiner. The spinal cord ends at L1 and so the spine is entered between L3-4 or L4-5 to prevent cord damage. Entry is made through a 25-gauge needle for anesthesia, and then a spinal needle is used to obtain cerebral spinal fluid (CSF). A manometer is used to measure opening and closing CSF pressure. Usually, 1-2 mL of CSF is collected for testing. The CSF is evaluated for appearance (pink for blood and yellow for bilirubin), pressure (increased in intracranial masses, meningitis, subarachnoid hemorrhage, and pseudotumor cerebri), microscopic evaluation (to evaluate for tumor cells, RBCs, and bacteria).

SYNCOPE, SEIZURES, AND EPILEPSY

The episodic loss of consciousness, or syncope, can herald the presence of serious systemic or neurologic disease. The list of possible causes of what the patient may describe as a "fainting spell" is quite extensive. Although many causes are somewhat benign, a history of even a single syncopic event should provoke an earnest attempt to uncover an underlying and serious disorder. Syncope is the result of a reduction of perfusion to the brain resulting from a loss of vasovagal tone. These "simple faints" are common at all ages and are rarely serious. More significant causes of syncope are cardiac dysfunction and cerebrovascular disease. Syncope must be differentiated from seizures, the other significant type of episodic loss of consciousness. While syncope is the result of a reduction in the blood supply to the brain, seizure activity is caused by a derangement in the synchronized discharges of the cerebral neurons. Both syncope and seizures produce a transient and often recurrent loss of consciousness, but the causes of both are strikingly different.

Syncope

Vasovagal syncope is the most common cause of simple faints. In this condition, factors such as emotional stress, pain, fright, hemorrhage, or prolonged standing cause a decrease in arterial blood pressure and pulse, leading to global hypoperfusion of the cerebral hemispheres.

Syncope most often occurs in a standing position and the onset of the episode is often heralded by a prodrome of light-headedness, tachycardia, nausea, and blurred vision. The patient will fall to the ground, appear pale, and both pupils will dilate. Once the patient is horizontal, the pulse rate will slow and it is not unusual to observe seizure-type activity with urinary incontinence. Because of this, epilepsy must be considered in the differential diagnosis of seizure activity during a syncopic event. Within seconds to minutes of an uncomplicated syncope, the patient will recover consciousness. A postsyncopic confusional state of severe fright and disorientation often occurs that lasts less than a minute. The most common recurrence of syncope is in the first 30 minutes of the first event when the patient attempts to stand.

On the basis of these characteristics, certain precautions should be followed to reduce the risk of injury during a syncope. As soon as a patient complains of light-headedness, dizziness, nausea, or profuse sweating, an attempt should be made to have him or her lie down in a horizontal and safe position. In this way, the risk of injury from a fall is minimized, and the horizontal position aids blood flow to the cerebral cortex and brainstem. Any constrictions around the neck such as neckties or a buttoned-up shirt should be loosened. An attempt should be made to hydrate the patient with water. Despite these maneuvers, the patient may still fall unconscious. If this occurs, all potentially dangerous objects in the environment of the unconscious patient should be removed in an effort to reduce injury in case seizure activity commences. A wet washcloth can be placed over the forehead of the patient or on the back of the neck. The pulse and respiration should be regularly monitored during unconsciousness to assure that a cardiac emergency is not imminent.

Simple syncope requires an evaluation by the primary care physician to exclude underlying cardiac, neurologic, and psychiatric disorders. The vast majority of simple syncopic events are the result of vasovagal causes or orthostatic hypotension. In orthostatic hypotension a loss of consciousness occurs when the patient rapidly rises from a sitting or lying position. This rapid shift in body posture results in a reduction of cerebral blood flow. This diagnosis is easily confirmed by a systolic blood pressure drop of 30 mmHg or a diastolic blood pressure drop of 10 mmHg when the patient attempts to stand. Orthostatic hypotension may be caused by hemorrhage, dehydration, drugs, multiple sclerosis, and prolonged bed rest. Successful treatment is best achieved by modification of the cause of the hypotensive state.

Syncope in a patient who has a history of heart or cerebrovascular disease is an ominous sign possibly heralding a cardiovascular or cerebrovascular event. Syncope may occur because of a rapid reduction in cardiac output resulting in cerebral hypoperfusion. Cardiovascular disorders that cause syncope include cardiac arrest, arrhythmia, aneurysm, and embolism among many others. Any patient who experiences a syncope while lying at rest or following exercise must have a physical examination to exclude heart and vascular issues.

True cerebrovascular disease is an uncommon cause of syncope. In basilar artery insufficiency a constellation of signs and symptoms occurs that includes diplopia, vertigo, drop attacks, and occipital headaches. These episodes are transient and brief and caused by brainstem ischemia. If left untreated, one fifth of all these patients will eventually develop stroke.

Innominate artery stenosis produces retrograde blood flow in the vertebral artery resulting in brainstem hypoperfusion. This process causes the classic "subclavian steal syndrome" when the subclavian artery is only 40% stenosed. This condition is diagnosed by the presence of transient syncope in patients who exhibit a difference in blood pressure between the right and left arms of at least 45 mmHg.

Other causes of syncope include migraine headaches, hyperventilation, coughing, and urination.

Seizures

A seizure is a loss of consciousness that occurs because of an abnormal neuronal discharge. This transient episode is indicative of a disturbance of normal cerebral function. During a seizure the patient typically experiences convulsions, but because of an unconscious state often has no memory of the episode. Convulsions may also occur in syncope and so it is essential to discriminate between the two disorders because they have widely disparate implications and therapies. In general, postsyncopic patients do not have a prolonged confusional state, whereas postictal seizure activity is associated with an extended period of disorientation. The longer the postictal state of agitation or confusion the greater the likelihood of seizure activity.

A neurologic evaluation of the seizure patient attempts to determine the cause of the event. The etiology may be neurologic or systemic. The most common neurologic causes of seizures include epilepsy, head trauma, stroke, cranial tumor, and meningitis. The most common systemic disorders associated with seizures include hypoglycemia, drugs, and eclampsia.

Epilepsy

Epilepsy is a group of disorders characterized by recurrent seizures. After an initial seizure event, only 30% to 50% of patients go on to have a second attack. If a second seizure occurs, however, 75% of these patients go on to have more seizures. More than 75% of all seizures are caused by idiopathic epilepsy (IE). IE usually begins in patients younger than 25 years. The diagnosis of epilepsy is made on the basis of witness verification of seizure activity with a prolonged postictal state, and hallmark abnormal EEG readings consisting of focal spikes or spike-and-wave discharges. Neuroimaging can exclude tumor or abscess as an underlying cause of the seizure activity. Blood studies should include serum glucose, calcium, fluorescent treponemal antibody absorption assay (FTA-ABS) and electrolytes, complete blood cell count, sedimentation rate, and renal function studies.

Tonic-Clonic Seizures

These "grand mal" seizures are episodes of loss of consciousness without warning. The tonic phase consists of contractions of the limb muscles producing limb extension and arching of the back for approximately 20 seconds. These movements may be accompanied by respiratory expiration and audible moaning. Breathing does not occur during the tonic phase, and cyanosis may result in pallor of the skin. After the tonic phase, a period of muscular contraction and relaxation that results in limb jerking occurs, known as the clonic phase. The clonic phase may last for a minute or longer. Breathing returns with resolution of the cyanosis at the start of the clonic phase. In the clonic phase the mouth may froth with saliva, and urinary incontinence may occur. Recovery from the grand mal seizure may take more than 20 minutes, and this delayed postictal stage is highly suggestive of epilepsy. In simple syncope, the postictal stage lasts only a minute or two.

Status Epilepticus

The state of status epilepticus establishes the state of medical emergency in relation to seizure activity. Most seizures are not medical emergencies. Status epilepticus is defined as seizure activity that lasts longer than 30 minutes without recovery, and this is considered a medical emergency.

Treatment of Seizures

Treatment is directed at the cause of the seizures. Once any underlying systemic or metabolic disorders are addressed the associated seizures cease. IE is treated with anticonvulsant drugs. Before drug therapy is started the diagnosis of IE must be assured. Once IE is established, the appropriate anticonvulsant drug is picked on the basis of the type of seizure activity. Rarely is a single seizure reason to start a medication. Drugs of first choice in controlling seizure activity include phenytoin and carbamazepine. Other anticonvulsant drugs include valproic acid and phenobarbital. Newer anticonvulsant medications include gabapentin, vigabatrin, and tiagabine. After 2 to 5 years of therapy, many patients express the desire to stop their anticonvulsant medications. The risk of recurrence is only 25% after medication is stopped, and so it is reasonable to try discontinuation, particularly in children. The drug is stopped by tapering during a 6-week period.

STROKE AND CEREBROVASCULAR DISEASE

Definition

A stroke is an acute neurologic deficit of the central nervous system that persists for at least 24 hours and is caused by a reduction in cerebral circulation.

Epidemiology

Each year in the United States, 750,000 new strokes occur. In addition, approximately 150,000 people die of stroke in the United States each year. In symptom-free men and women aged 30 to 60 years, untreated systemic hypertensive patients were seven times more likely to develop a stroke than nonhypertensive patients.

Risk Factors

Age is the leading risk factor in stroke, with two thirds of all strokes occurring in patients older than 65 years. Strokes occur more commonly in men than women,

and strokes occur more frequently, at an earlier age, and are more severe in African-Americans than in whites. The risk of stroke is greater in patients with diabetes, obesity, systemic hypertension, and hypercholesterolemia. Heavy alcohol consumption and cigarette smoking are both significant personal behaviors that increase the risk of stroke. The use of oral contraceptives dramatically increases the risk of stroke in young women.

Genetic Factors

No doubt exists that genetic and environmental factors influence the relative risk of stroke in any individual patient. Genetic factors influence the health of the blood vessels, the efficiency of the heart, and the biochemical makeup of the blood. Several monogenetic syndromes have been identified that influence the risk of stroke. In general, a particular gene produces a protein yielding a specific stroke syndrome. One example is cavernous angioma syndrome, which involves the KREV interaction trapped 1 protein, produced by the *KRIT1* gene. Another syndrome modifies the risk of carotid and cardiogenic stroke because of the protein phosphodiesterase 4D, which is produced by the gene *PDE4d.* In this syndrome, some haplotypes increase and others decrease the risk of stroke.

Etiology

The underlying etiology of a stroke is either ischemia or hemorrhage. Ischemia accounts for approximately two thirds and hemorrhage for approximately one third of all strokes.

Ischemia can be produced by embolism or thrombosis. Embolism represents occlusion of the cerebral artery by a thrombus generated at a distant site such as the carotid artery or the heart. Thrombosis represents an occlusion of a cerebral artery caused by pathological processes formed at the site of the occlusion. The major risk factor for ischemia is atherosclerosis, and this is heavily influenced by systemic hypertension. Other risk factors for ischemia include diabetes, hypercholesterolemia, migraine headache, cigarette smoking, and the use of oral contraceptives. Inflammatory disorders such as temporal arteritis and systemic lupus erythematosus also increase the risk of ischemia.

Hemorrhage can cause a stroke by destroying brain tissue because of toxicity, pressure effects on intracranial structures, increase in intracranial pressure, or compression of the vascular supply leading to ischemia. The symptomology of each of the four sites of intracranial hemorrhage (intracerebral, subarachnoid, subdural, and epidural) is fairly unique. After onset, a hemorrhagic stroke worsens in minutes to days because of edema surrounding the area of bleeding.

Pathology

Ischemia interrupts the blood flow to the brain. Oxygen and glucose cannot reach the brain tissues, which results in cell death. Ischemia results in energy failure of the cells with subsequent loss of membrane potential control. Transmembrane ion potentials break down and potassium leaks out of the cells, stimulating the release of glutamate. This process causes sodium to enter the neuronal cell bodies. The neuronal cells swell, their mitochondria become injured, free radicals are formed, and enzymes are activated. The plasma membranes of the cells break down, and the neurons die.

In hemorrhagic stroke, the neurologic deficit is caused by bleeding and edema. These two factors compress tissue and rarely destroy brain cells. Considerable return of some neurologic function is therefore possible in hemorrhagic stroke.

Symptomology

Stroke is characterized by the acute onset of symptoms as documented in the history. If the symptoms are maximal at the time of onset, then an embolic etiology is implied. If the symptoms increase over time, usually minutes to hours, then a progressive arterial thrombosis or recurrent emboli is the most likely cause. Neurologic deficits that progress during weeks to months are most suggestive of a space-occupying lesion, inflammatory disorder, or degenerative disease. Clear evidence of a stroke based on signs and symptoms should prompt a neurologic exam to pinpoint the anatomic location of the lesion.

The focal symptoms often suggest the area of the brain affected by the stroke. The pattern of deficits reflects ischemia to a specific area of the brain. In more complicated stroke, such as from hemorrhage, the secondary effects of spreading edema and increased intracranial pressure may result in complicated and unpredictable signs and symptoms. A stroke is almost always isolated to the side of the brain opposite the deficit.

A patient who is seen with cognitive deficits such as aphasia, paraxial, and agnosia most likely has had a stroke to the anterior circulation of the brain. This area includes the branches of the internal carotid artery that supply the cerebral cortex, subcortical white matter, basal ganglia, and the internal capsule. Strokes affecting the anterior cerebral artery cause contralateral paralysis and sensory loss of the leg, and loss of bladder control. Strokes of the middle cerebral artery can cause aphasia and contralateral hemiparesis of the face, hand, and arm. Occlusion of the internal carotid artery (which causes one sixth of all strokes) causes contralateral hemiplegia, homonomous hemianopsia, and aphasia. Occlusion of the posterior cerebral artery

causes vertical gaze palsy, oculomotor nerve palsy, internuclear ophthalmoplegia (INO) homonomous, and hemianopsia of the contralateral visual field.

A patient who is seen with vertigo, nausea, vomiting, cranial nerve palsies, and ataxia, has involvement of the brainstem implying the posterior circulation. This region includes the vertebral and basilar arteries and their branches, which supply the brainstem, cerebellum, thalamus, occipital lobe, and temporal lobes. Occlusion of the basilar artery can cause abducens nerve palsy, vertical nystagmus, bilateral papillary miosis, and coma. Stroke patients who are seen with ocular nerve palsies or nystagmus invariably have had a brainstem infarct secondary to occlusion of the posterior circulation.

Deep cerebral hemorrhages typically produce contralateral sensory and motor defects. A homonomous hemianopsia is a typical occurrence after a deep cerebral hemorrhage. If the midbrain is affected, the eyes may become esotropic and experience vertical gaze palsy. Aphasia can be expected if the cortical language areas are affected.

Hemorrhages in the white matter produce deficits that coincide with loss of specific lobular function. These hemorrhages typically produce headache, vomiting, hemiparesis, aphasia, and visual field deficits.

A hemorrhage within the pontine area produces pinpoint pupils, horizontal gaze palsy, downbeat nystagmus, and quadriparesis.

Cerebellar hemorrhage produces headache, dizziness, and vomiting. The patient will not be able to stand or walk. In cerebellar hemorrhage the patient will not be able to look to the side of the lesion, and the pupils are miotic but reactive.

Transient Ischemic Attack

Transient ischemic attacks (TIAs) are episodes of neurologic deficits that imply a stroke but only last an average of 30 minutes. A hallmark of the TIA is complete resolution of the symptoms and signs. The most common cause of repeated TIAs is thrombosis or embolism of the cerebral vasculature. If recurrent TIAs differ from episode to episode, the most likely source of the emboli is extracranial, usually the heart.

TIA is a significant predisposing factor for stroke. Approximately one third of all untreated patients with TIAs go on to experience a stroke within 5 years.

A significant and common TIA symptom is unilateral blur-outs of vision that last for fleeting seconds to minutes. This history mandates a retinal examination to exclude the presence of a Hollenhorst plaque within the retinal arterial tree of the involved eye. The presence of such a plaque is significant, because it heralds a strong risk for cerebral stroke. In one study, approximately 50% of untreated patients with Hollenhorst plaques went on to have a significant intracranial vascular event within 5 years. The presence of a Hollenhorst plaque mandates auscultation of the carotid arteries to exclude the presence of an arterial bruit. Carotid stenosis is very common in the elderly, because almost one third of all men older than 75 years have some narrowing of the carotid artery. If an associated bruit is found, then the area on the neck of the patient should be circled in indelible ink and the patient sent within the week to the primary care physician. If possible, a photograph of the Hollenhorst plaque should be supplied to the family physician, because this tends to help motivate the coordination of a vascular evaluation.

Minor Stroke

In cases of minor stroke, neurologic deficits persist longer than 24 hours but resolve completely within one week. The minor stroke is also known as reversible ischemic neurologic deficit (RIND).

Treatment

The following modalities are used to treat cerebrovascular disease.

Antiplatelet Therapy

Antiplatelet agents inhibit the enzyme cyclooxygenase-1, thus preventing the platelet-aggregating properties of thromboxane A2. The result is the interference of platelet functioning with resultant reduction in the risk of embolism, blood clotting and occlusive stroke. These agents include aspirin, ticlopidine, clopidogrel, sulfinpyrazone, and dipyridamole.

Aspirin

Aspirin has been shown in several studies to reduce the risk of TIAs, stroke, and death when given to individuals who experience repeated TIAs or have evidence of minor stroke. Most often in the United States a dose of 325 mg of aspirin is used on a daily basis. In middle-aged men, aspirin was not shown to reduce the risk of stroke when administered to those who had no previous history of stroke or TIA. In these same individuals, aspirin was shown to reduce the risk of heart attack.

Ticlopidine

At a dosage of 250 mg, twice daily orally, ticlopidine is an antiplatelet medication that is more effective than aspirin in preventing stroke. Ticlopidine has also been shown to be more effective than aspirin in reducing mortality in patients with TIA and mild stroke. The disadvantages of ticlopidine include its expense and the undesirable side effects of skin rash and diarrhea.

Clopidogrel

At a dosage of 75 mg, once daily orally, clopidogrel is a antiplatelet agent that reduces the incidence of myocardial infarction and ischemic stroke.

Dipyridamole

The extended release form of dipyridamole, 200 mg, taken with 25 mg of aspirin twice daily, has been recommended to prevent stroke in patients with previous TIA or stroke.

Anticoagulant Therapy

So-called "blood thinners" are indicated in patients when cardiac embolism is the cause of TIAs. The significant potential hazard of these agents is the risk of intracranial hemorrhage, particularly in elderly, hypertensive patients. These anticoagulants include heparin and warfarin.

Heparin. Heparin is an anticoagulating agent used for short-term use in acute vascular situations. It is administered via intravenous infusion.

Warfarin. Warfarin is begun at a daily dosage of 1 to 15 mg orally, simultaneously with heparin, and then continued after heparin is discontinued. Warfarin is used in the long-term care of the patient with TIA or a history of stroke.

Carotid Endarterectomy

This surgical technique is performed on a stenotic carotid artery in the neck. The goal of this surgery is to remove a thrombus from the artery in an attempt to reduce the risk of stroke in patients who have TIAs and 50% to 99% carotid stenosis. Endarterectomy plus aspirin has been shown to be superior to aspirin alone in stroke prevention.

Antiplatelet agents are the treatment for asymptomatic carotid bruit or stenosis of the carotid artery. Surgical endarterectomy may be equally effective, but it carries greater risks. Some studies have shown an operative risk of mortality of 5% associated with carotid endarterectomy. In addition, the CAVATAS and SAPPHIRE studies have shown that newer techniques using transluminal angioplasty for the placement of metal stents in the carotid and vertebral arteries are safer than endarterectomy. These stents maintain luminal patency, but a greater risk of restenosis exists when compared with endarterectomy.

Thrombolytic Therapy

This therapy makes use of agents that lyse the incontaining clots found in cerebrovascular thrombotic lesions. The intravenous use of these agents within 3 hours of the onset of symptoms seems to reduce disability and mortality from ischemic stroke according to some studies. The serine protease tissue plasminogen activator (t-PA) is administered by intravenous infusion during a 1-hour period, but carries a significant risk of hemorrhage. This agent, as well as the other major thrombolytic agent, urokinase, should never be considered if any evidence is present that the stroke is hemorrhagic in nature.

The treatment of TIAs from a cardiac, carotid, or intracranial or vertebrobasilar source includes both antiplatelet agents and the use of anticoagulants.

Any stroke in evolution requires anticoagulants. Completed strokes from a cardiac source are treated with antiplatelet and anticoagulant medications. A stroke from a carotid source is treated with antiplatelet agents, anticoagulants and thrombolytics. Endarterectomy is often also considered in these cases. In intracranial or vertebrobasilar source of the completed stroke requires antiplatelets, anticoagulants and thrombolytic agents.

The treatment of intracerebral hemorrhage involves cerebellar or cerebral decompression. These procedures allow a reduction of the mass effect of the hemorrhage and a realignment of the intracranial structures.

MOTOR DEFICITS

Motor deficits represent weakness caused by a disorder of the neuromuscular system. In general, the abnormality will be isolated to the nerve, the muscle, or the neuromuscular junction. A sudden onset of weakness implies a vascular, metabolic or toxic process. A chronic onset of days to weeks implies an inflammatory, infectious, or neoplastic disturbance.

Muscular weakness invariably occurs after stroke, and typically has an acute onset. Spinal cord processes such as infection, multiple sclerosis, tumor, and disk herniation often are seen with subacute weakness. Myasthenia gravis and other disorders of neuromuscular transmission may also cause weakness.

Multiple Sclerosis

Multiple sclerosis (MS) is a disease of young adults with a peak incidence between ages 20 and 40 years. MS affects women twice as often as men, and the risk of MS increases with increasing distance from the equator. A strong genetic association exists between MS and the HLA DR2 antigen. Genetic studies support the hypothesis that no single gene is responsible for the development of MS, however. In the United States, whites are twice as likely to acquire MS as nonwhites.

MS is characterized by the development of focal areas of demyelination with axonal damage. The lesions are limited to the white matter, the spinal cord, and the optic nerve. An immune mechanism is thought to be the basis for the development of the lesions in MS, because antibodies are directed against myelin

antigens. This theory is supported by the finding of accumulated macrophages in the areas of myelin loss. As the immune attack commences, the axons are stripped of their myelin sheaths, which results in slower nerve conduction. Histological studies reveal atrophy of the optic nerve, optic chiasm and spinal cord axons. Neurologic deficits develop secondary to this derangement in nerve conduction.

The initial symptoms of MS include focal numbness, tingling, weakness in a limb, diplopia, and unilateral blurred vision. At the initial doctor visit, more than one third of MS patients exhibit paresthesias, one third have gait disorder, and approximately one sixth have visual disturbances. Of patients, 10% experience "benign" MS, with no debilitating symptomology during the course of their disease. Of patients, 85% experience extensive exacerbations and remissions with debilitating progression of the disease. In evaluating the entire population of MS patients, the disease shortens the lifespan by a few years at most. In untreated MS, one fifth of all patients could not walk freely within 5 years of onset.

Visual Symptoms

Optic neuritis produces blurred vision in the involved eye, and is often the first symptom of MS experienced by the patient. The most common neuroophthalmologic manifestation of MS is INO, composed of a lag of the contralateral eye on horizontal excursions (i.e., left eye lags when looking to the right), and impaired convergence.

Dizziness

Early in the course of MS, patients often describe a feeling of unsteadiness. This is a vague symptom, but combined with visual blurring, it may point to a more significant diagnosis. As the disease progresses, patients may describe attacks of spinning vertigo. Nystagmus in a patient with vertigo complaints should prompt an evaluation to consider MS. Patients may also describe peripheral neuropathy-like symptoms including pins and needles in the digital extremities. The Lhermitte sign, described by patients as an electric shock that radiates down the arms or back when bending the neck, is pathognomonic of MS.

The course of the disease is characterized by extreme exacerbations and remissions. As the course of the disease continues, the patient becomes disabled with weakness, sensory disturbances, unsteady limbs, loss of vision, and urinary incontinence. End-stage MS is characterized by optic atrophy, nystagmus, and cerebellar deficits in the limbs.

Laboratory support for the presence of MS is gained by CSF evaluation. CSF protein electrophoresis demonstrates the presence of oligoclonal bands that are produced by abnormal immunoglobulin G (IgG) synthesis. CSF evaluation through lumbar puncture has now been almost entirely supplanted by neuroimaging in the diagnostic evaluation for MS.

The presence of MS is defined as the localization of central white matter lesions occurring in two different places at two different times. MRI is invaluable in visualizing abnormal regions of high signal intensity indicative of MS. These lesions are typically multiple, ovoid, white matter plaques located in the periventricular region. These plaques may be confused with "unidentified bright objects," or UBOs, the cause of which is related to heavy smoking, systemic hypertension, and migraine headaches.

The disability and relapses characteristic of MS may be prevented by the use of interferon beta-1a. The use of high-dose interferon during a 4-year study definitively reduced the rate of relapse when compared with a lower dosage. Interferon alters the mechanism of antigen presentation in MS by altering the mechanism of antigen presentation. This process seems to reduce the myelin reactive T-cell activation by preventing the T cell from crossing the blood-brain barrier. The inflammation within the myelin of the white matter is thus ultimately reduced.

Azathioprine, an immunosuppressant, has been shown to decrease relapse rates with minimal toxic effects.

Reduction of the rate of MS relapse can be achieved with injections of interferon or glatiramer acetate. This polypeptide acts on the aberrant immune response by altering the mechanism of antigen presentation in MS. It reduces relapse rates in patients with MS.

Corticosteroids are used to speed recovery from a relapse, but use of steroids has no effect on the development of the overall disease. The course of MS is unpredictable, although the most favorable outcomes are seen in women younger than 40 years who are seen with visual dysfunction. The worst prognosis is seen in men who are diagnosed with the disease later in life, and whose earliest dysfunction is cerebellar.

Myasthenia Gravis

A disorder of neuromuscular transmission, myasthenia gravis (MG) is characterized by abnormal weakness of the voluntary muscles. More women than men are affected. The onset in women peaks between the ages of 20 to 40 years, and in men the peak incidence occurs between the ages of 40 and 60 years.

The onset of symptoms is heralded by an insidious fatigability of the external ocular muscles and other craniofacial muscle groups. In 60% of cases, the first clinical signs involve weakness of the ocular muscles that results in ptosis and diplopia. In fact, more than 90% of MG cases involve the extraocular muscles. No pupillary effects occur in MG. Of these

patients, 90% go on to more generalized weakness within 2 years.

The patient may complain of difficulty chewing and swallowing. Dramatic weakness of the normally powerful movements of the major muscles of the limbs is also present. In time, the respiratory muscles can become impaired. The condition is characterized by exacerbations and remissions. The symptoms of MG are worsened by pregnancy and underlying infection. Drugs such as propranolol, lithium, tetracycline, and aminoglycoside antibiotics worsen the myasthenic condition and should be avoided in these patients.

MG is caused by an immune-mediated disorder. In approximately 80% of MG patients, detectable antibodies to the postsynaptic acetylcholine (ACh) receptor are present. Loss of the receptor in the postsynaptic muscle membrane prevents depolarization of the postsynaptic muscle membrane resulting in muscle weakness and fatigue. An immune-mediated disorder is also suspected in the remaining 20% of patients who do not exhibit ACh-receptor antibodies.

The diagnosis of MG begins with the high degree of suspicion raised by the clinical signs and symptoms. The examiner can confirm involvement of the upper lids by asking the patient to sustain an upgaze posture and noting a worsening of the ptosis within 2 minutes.

Electromyography (EMG) is of significant diagnostic importance when evaluating a patient for MG. The classic electrodiagnostic pattern in MS is known as the electrodercremental response. Reduction in the action potential size is present and reverses to normal when edrophonium chloride (Tensilon) is administered to the patient.

Pharmacological testing for MG involves anticholinesterase drugs to demonstrate a temporary improvement in muscle power. The Tensilon test is conducted by the intravenous administration of 10 mg of edrophonium and the subsequent observation of approximately 5 minutes of muscular strength improvement. Tensilon is a acetylcholinesterase inhibitor.

An alternative to edrophonium is the intramuscular injection of neostigmine that in MG patients improves muscular strength for as long as 2 hours.

MG is often found associated with tumor of the thymus (in 15% of patients with MG), thyrotoxicosis, rheumatoid arthritis, and lupus erythematosus. These conditions should be excluded by a complete physical examination with laboratory testing and radioimaging studies.

The treatment of MG includes the use of surgery, medications, and plasmapheresis. Pyridostigmine is an anticholinesterase drug given at a dosage of 60 mg, four times daily orally, for symptomatic improvement.

If the patient is younger than 60 years and does not respond well to pyridostigmine, then a surgical thymectomy may lead to slowly improving symptomatic relief. The mechanism by which thymectomy leads to symptomatic improvement is not yet understood. More than 60% of patients improve with thymectomy, but it is only offered to patients younger than 60 years.

If the patient responds poorly to pyridostigmine and thymectomy, then corticosteroids may be helpful. In fact, many think that corticosteroids are the first treatment of choice to induce remission of the autoimmune element of MG. Oral prednisone is administered, but the patient must be watched closely for transient respiratory difficulty. Steroids are effective in inducing remission of MG in 80% of cases.

If MG exacerbates despite these treatments, then azathioprine has been found to be helpful. The therapeutic benefits of azathioprine may take as long as a year from initiation.

Plasmapheresis, or plasma exchange, permits temporary improvement in cases of rapidly worsening MG or before surgery. This technique removes acetylcholine receptor antibodies from the blood and produces rapid but short-lived improvement in symptoms.

The majority of patients with MG achieve well-controlled tolerance of their muscle weakness with drug and surgical intervention. The mortality associated with MG is mostly related to aspiration pneumonia caused by respiratory weakness.

Muscular Dystrophies

This group of disorders is characterized by muscle weakness and muscle wasting (Table 17-1). These inherited disorders exhibit variations in age at onset, muscle involvement, rate of progression, and prognosis. Muscular dystrophies result in deformities of the musculoskeletal system and muscular contractures. Treatment of these myopathic disorders encompasses targeted physical therapy and orthopedic surgeries.

Ocular Dystrophy

This dystrophy is inherited as an autosomal dominant disorder that causes deletions in the DNA of the mitochondria. Most patients are affected when they are younger than 30 years. The earliest manifestation of ocular dystrophy is ptosis. Eventually, external ophthalmoplegia occurs with facial weakness. As the dystrophy slowly develops, the limb muscles may weaken. The prognosis of ocular dystrophy is unknown, and the condition is rare and not well studied.

Oculopharyngeal Dystrophy

Like ocular dystrophy, this disorder is autosomal dominant in its inheritance pattern. It is found most commonly in Quebec, Canada, and the American southwest. It is similar to ocular dystrophy, but the earliest manifestations typically occur in patients between the

TABLE 17-1 CLASSIFICATION OF THE MUSCULAR DYSTROPHIES

TYPE	INHERITANCE	AGE AT ONSET	PROGRESSION
Duchenne's	X-linked, recessive	Early childhood	Rapid, fatal
Becker's	X-linked, recessive	Second decade	Slow, nonfatal
Limb-girdle	Autosomal, recessive	Variable, first to sixth decades	Variable, disability usual
Facioscapulohumeral	Autosomal, dominant	Variable, childhood to late adulthood	Benign, not progressive
Oculopharyngeal	Autosomal, dominant	Fifth decade	Slowly progressive
Ocular	Autosomal, dominant	Fifth decade	Slowly progressive
Distal	Autosomal, dominant	Middle to late adulthood	Slowly progressive
Myotonic	Autosomal, dominant	Variable	Slowly progressive

ages of 30 to 50 years. Like ocular dystrophy, the earliest clinical signs are ptosis and external ophthalmoplegia. Facial and limb weakness often follow. Dysphagia can be so debilitating that nasogastric feeding is necessary. Like ocular dystrophy, this is a rare and understudied condition.

Myotonic Disorders

Myotonia represents a group of disorders that are characterized by muscle stiffness. This condition is caused by an inherited abnormality of the muscle fiber membrane, or sarcolemma. The muscle stiffness results from the inability of the muscle to relax immediately after contraction.

Myotonic Dystrophy

This autosomal dominant disorder typically manifests in the young adult. The defective gene is located in chromosome 19q13.2-12q13.3. Expression of this gene causes a defect in the protein myotonin-protein-kinase. The ocular signs of myotonic dystrophy include ptosis and cataract formation. The facial and limb muscles begin to weaken, and premature frontal balding, cardiac abnormalities, and cognitive changes in intelligence often occur. The treatment of myotonic dystrophy makes use of quinine sulfate, 300 to 400 mg, three times daily. Other medications that are useful in myotonia include procainamide and phenytoin. No treatment exists for the muscular weakness associated with myotonia.

Dermatomyositis

This inflammatory myopathy exhibits destruction of the muscle fibers. In addition, inflammatory infiltration of the muscles occurs. Dermatomyositis represents a microangiopathy of the skin and muscles with widespread destruction of capillaries caused by an immune response that leads to muscle ischemia. As such, it is understandable that dermatomyositis is associated with such autoimmune disorders as Sjögren's syndrome, lupus erythematosus, and rheumatoid arthritis. The myopathy is characterized by an erythematous rash that covers the eyelids known as the heliotrope rash. In patients of any age, the limbs proximal to the body become weak and begin to waste. The muscles become painful, and respiration becomes difficult. Laboratory testing reveals an elevated serum creatine kinase, and electromyography reveals fairly characteristic patterns. Muscle biopsy is essential for the diagnosis. Dermatomyositis is treated with prednisone during a 2- to 3-year tapering period. Immunoglobulins may be administered intravenously instead of steroid treatment, and methotrexate also has been shown to be an effective alternative to prednisone. Alternative and newer immunosuppressants such as mycophenolate mofetil are now under study. Physical therapy is a valuable adjunct to pharmaceutical intervention.

MOVEMENT DISORDERS

Tremor

Tremor is characterized by rhythmic movements of a limb. Tremors may be caused by anxiety, physical activity, drugs, inherited disorders, cerebellar disease, and parkinsonism. Intention tremor is an uncontrollable rhythmic movement elicited during physical activity.

Chorea

Unlike the rhythmic, predictable movements of tremor, chorea is characterized by the spastic, irregular, and episodic jerking of disparate muscle groups. Extreme facial grimacing and tongue rolling are often present. A lurching type of gait with swaying to one side or the other may be present. Speech volume becomes just as unpredictable and varied. Interestingly, chorea does not occur during sleep. Chorea appears because of loss of cells in parts of the brain; in particular, the caudate nucleus and putamen. Chorea is characteristic of Wilson's disease and cerebral palsy, and may result from drugs, lupus, AIDS, stroke, thyrotoxicosis, and subdural hematoma.

Tics

These involuntary movements are characterized by quick and recurrent movements. These movements are made worse by stress and anxiety, but can be suppressed for short periods of time. Tics disappear during sleep.

Parkinsonism

This very common disorder affects approximately 2 of every 1000 people in the United States. The major risk factor for parkinsonism is advancing age. Tremor, rigidity, and abnormal gait characterize the classic parkinsonism patient. Hypokinesia, or the slowing of movements, also causes an immobility of the facial muscles, causing the classic "Parkinson stare." Patients may complain of blepharospasm, or an involuntary closure of the eyelids. In addition, a fluttering of the eyelids, or blepharoclonus, may occur. Blepharoclonus should be readily differentiated from myokymia, an involuntary and benign fluttering of an eyelid that is unrelated to parkinsonism.

This condition is most commonly idiopathic and known as Parkinson's disease, but may also be caused by encephalitis, drugs, and toxicity.

In parkinsonism, a loss of cells and an essential protein (alpha-synuclein) occurs in the brainstem. In addition, it appears that an imbalance exists between two antagonistic neurotransmitters, acetylcholine (ACh) and dopamine, in the corpus striatum. This derangement of the normal balance of neurotransmitters would explain the abnormal motor movements characteristic of parkinsonism.

Although no treatment is necessary in early parkinsonism, in the later stages of the disease severe debilitation may be avoided by restoring the normal ACh-dopamine balance. To this end, muscarinic anticholinergic drugs such as trihexyphenidyl and benztropine suppress the effects of ACh and are useful in minimizing rigidity and tremor.

Levodopa enhances dopaminergic transmission, reduces tremor and rigidity, but also causes hypokinesia. Sinemet is a commonly prescribed parkinsonism treatment that combines levodopa with carbidopa. Levodopa administration is contraindicated in patients with narrow-angle glaucoma.

The dopamine agonists bromocriptine, pergolide, pramipexole, and ropinirole stimulate dopamine D2 receptors.

If patients are unresponsive to medical treatment, then surgically induced lesions to the internal segment of the globus pallidus will reduce tremor and rigidity. An alternative to surgery is high-frequency deep brain stimulation, which has been found to reduce all clinical manifestations of the disease.

Progressive Supranuclear Palsy

This progressive disorder represents degeneration of the cortical gray matter. Histologically, degeneration of the neurons occurs, with the presence of neuronal "tangles" in the midbrain and areas of the cerebellum. Biochemically, dopamine levels decrease.

The earliest symptoms include gait abnormalities, drop falls, and supranuclear ophthalmoplegia. The ophthalmic manifestations include vertical and, later, horizontal gaze palsy. The facial muscles become weak, and swallowing becomes difficult. Dementia is characterized by memory issues, personality changes, and slowed cognitive functions.

No treatment exists for progressive supranuclear palsy, and therapeutic measures are aimed at temporary improvement of speech, gait, and rigidity.

Wilson's Disease

This condition is inherited as an autosomal recessive disease of copper metabolism. The condition is caused by a number of genetic mutations that cause derangement of the copper-transport protein ceruloplasmin. Without proper binding and transportation a significant amount of copper enters the general circulation and deposits in the eye, brain, liver, and kidney. As copper accumulates in the mitochondria of these target organ cells, free radical formation and oxidation lead to tissue damage.

Wilson's disease begins in the young with an average onset by age 11 years. The most common finding in Wilson's disease is the Kayser-Fleischer ring of the cornea. These appear as brown, circular deposits in Descemet's membrane, where they represent abnormal deposits of copper in the cornea.

As the disease progresses, anemia, chronic liver cirrhosis, enlargement of the spleen, and thrombocytopenia may occur. Renal tubular damage may result in elevated amino acids in the urine.

As the cerebellum becomes involved, tremor, facial tics, rigidity, and difficulty swallowing may result. Eventually, dementia may be manifested by mental slowness, memory issues, and personality changes.

Treatment of Wilson's disease is directed at removal of the copper from the organs. To this end, penicillamine may be effective, because it is a copper-chelating agent.

INCREASED INTRACRANIAL PRESSURE

The brain has a limited ability to compensate for an increase in intracranial volume due to its position inside the rigid skull. In addition, 90% of the cranial cistern is brain, and only 10% is fluid. Therefore, any process that compresses, shifts, or distorts brain tissue causes an almost immediate rise in intracranial pressure (ICP).

As ICP rises, arterial blood flow is compromised, which leads to ischemia and edema of brain tissue. If the etiology is asymmetric, such as a unilateral tumor, then brain tissue may shift across a fixed intracranial structure leading to herniation.

Significant signs and symptoms are related to an increase in ICP. It is essential to recognize these, because elevated ICP can be a life-threatening medical emergency.

The earliest clinical symptom of an increase in ICP is lethargy and fatigue. This vague symptomology rarely provokes alarm, except when it is combined with complaints of an inability to stay awake. These are all early signs that the patient is slipping into coma. Any patient who complains of a decreasing level of consciousness and decreased response to stimuli should have an immediate neurologic evaluation. Often a member of the patient's family provides the key details describing this descent into coma. Immediate neurologic signs to evaluate include pupils, eye movements, limb mobility, and breathing.

As pressure builds up in the brain, the papillary reactions may change. As cranial nerve (CN) III becomes involved the pupils become irregular and respond poorly to light stimulation. If the medial longitudinal fasciculus (MLF) is affected then eye movements become abnormal. Finally, as pressure continues to elevate, limb paralysis ensues.

As the patient slips into coma, respiration patterns change. The rate and depth of respiration increase, and in some cases there is constant hyperventilation. In other situations intermittent apnea is present.

Causes of ICP include brain tumor, brain abscess, encephalitis, AV malformations, MS, and pseudotumor cerebri.

Pseudotumor Cerebri

Pseudotumor cerebri (PTC) is characterized by an increase in intracranial pressure. This condition most often affects young, overweight women. Many of the patients report a recent, relatively fast and undesired weight gain of as much as 40 pounds within 6 months of presentation.

Patient symptoms include dull, severe, and progressive headaches, and possible diplopia. The diplopia is horizontal and results from a lateral rectus muscle weakness. Other related symptoms include tinnitus and transient visual obscurations.

Ophthalmoscopy will reveal papilledema with nasal blurring of the optic disc. Visual fields taken immediately and quickly will reveal bilateral enlargement of the blind spots associated with concentrically contracted peripheral fields.

The signs of PTC are ominous and reminiscent of the expected clinical picture manifested by intracranial space-occupying lesions. No true malignancy is associated with PTC, however, hence the name *pseudo*tumor cerebri.

The underlying cause is unknown, although drugs such as antibiotics, oral contraceptives, steroids, NSAIDs, hormones, and anesthetics may induce the syndrome. PTC is often related to pregnancy and menstrual disturbances.

The condition is often referred to as benign idiopathic intracranial hypertension, but the condition may be far from benign. An MRI is mandatory to exclude the diagnosis of brain tumor.

The treatment of PTC involves weight loss, low-salt diet, the use of diuretics and headache management. During treatment the patient should be routinely monitored with visual fields. As papilledema resolves, the size of the blind spot of the visual field will reduce in size back to normal. If the patient is unresponsive to medical therapy, a CSF shunt procedure is mandatory.

Treatment of Increased ICP

The treatment of increased ICP does not depend on etiology, and extensive testing that may delay initiation of therapy does not improve the outcome. Treatment modalities for increased ICP are described in the text that follows.

Vascular Therapy of Increased ICP

A decrease in ICP can be achieved by reducing the total cerebral blood volume. To achieve this goal, hyperventilation, or the voluntary increase in respiratory rate, is used to induce vasoconstriction. Hyperventilation decreases CO_2 pressure, thus inducing vasoconstriction. Vasoconstriction in turn reduces cerebral blood volume, and a reduction in ICP follows. Reduction of ICP occurs within 30 minutes of hyperventilation, but the technique is effective only for short-term therapy.

Osmotic Therapy of Increased ICP

Osmotic agents induce water to move from the cells and interstitium to the plasma, thus reducing the water volume of the brain. The overall affect of this osmotic gradient is to reduce brain volume and ICP. In addition, by diluting the plasma the blood viscosity reduces thus preserving cerebral perfusion. Osmotics also have the added benefit of reducing cerebral spinal fluid (CSF) production and thus further reducing ICP. Mannitol solution is administered, and its desired effect usually achieved within 20 minutes. One administration lasts about 6 hours. Doses are given every 4 hours, although the effectiveness of mannitol reduces with time. In addition to osmotic agents, diuretics may be administered to enhance the ICP decrease.

Metabolic Therapy of Increased ICP

Cell injury and death result in increased oxygen delivery to the brain, resulting in undesirable free radical production. By reducing the metabolic need of the brain cells, blood flow to the brain is reduced, which in turn reduces oxygen delivery to the tissues. Barbiturate anesthesia reduces brain metabolic demand and therefore ICP, but it can have serious cardiac side effects.

Surgical Intervention of Increased ICP

Hemicraniectomy is a surgical technique useful in cases of increased ICP secondary to lobular tumor. This approach allows expansion of the involved lobe and a reduction in ICP in cases in which medical approaches have failed to reduce the ICP.

BRAIN TUMOR

Tumors of the brain may be malignant or benign (Table 17-2). Benign tumors may cause severe and life-threatening effects because of compression, hormonal production, or hemorrhagic effects.

Glioma

The most common malignant brain tumor in the U.S. population is the glioma. Low-grade glioma, such as the astrocytoma, is usually found in patients aged 5 to 30 years. The recommended treatment is observation, and the survival rate is usually 5 to 10 years.

Grade III anaplastic gliomas occur at ages 30 to 50 years, and with radiation and chemotherapy survival is usually 3 to 4 years.

Grade IV glioblastomas usually occur in patients older than 50 years, and with radiation and chemotherapy survival is at best 1 year.

It is impossible to remove all of the glioma surgically because of its infiltrative nature. In addition, total removal may cause severe neurologic deficits that are not compatible with life. Therefore, some neurosurgeons perform subtotal removal, which preserves maximal neurologic integrity while reducing symptoms related to compression.

Meningioma

These benign tumors arise from the arachnoid meningeal cells. They most often occur with increasing age and in women more than men. Meningiomas are very common, composing one seventh of all intracranial tumors. They are located in the meningeal covering the hemispheres, along the sphenoid bone along the base of the skull and the faux cerebri between the two hemispheres.

TABLE 17-2 COMMON TUMORS OF THE CENTRAL NERVOUS SYSTEM AND THEIR PROBABLE CELLS OF ORIGIN

TUMOR	CELL OF ORIGIN
Nerve Cell Tumors	
Ganglioneuroma, ganglioglioma	Neurons
Medulloblastoma	Immature neurons
Glial Cell Tumors	
Astrocytoma (benign)	Astrocytes
Glioblastoma (malignant)	Astrocytes
Oligodendroglioma	Oligodendroglia
Ependymomas	Ependymal cells (lining of ventricles)
Meningioma	Arachnoid mater
Pituitary Gland Tumors	
Craniopharyngioma	Rathke's pouch remnants
Pituitary adenoma	Pituitary gland cells
Tumors on Non-Neural Elements	
Hemangioblastoma	Endothelial cells (lining of blood vessels)
Lymphoma	White blood cells
Melanoma	Pigment cells
Teratomas	Germ cells

Meningiomas grow slowly and attain large sizes before symptoms are noticed. Early symptoms depend on location. Occipital meningiomas may produce bilateral, congruous visual field defects. One case study by this author revealed a left superior congruous scotoma resulting from a right, inferior occipital meningioma. The patient detected his bilateral positive scotomas when, on striking a golf ball, he noted that the ball disappeared as it rose up and to his left. The patient, being an artist by avocation, drew his own visual fields that exactly matched his later results with Goldmann bowl perimetry testing. In addition, the patient noted that on looking down at his golf ball, he noted color vision distortion, with the left part of the ball fringed in red and the right part of the ball fringed with green. The patient had surgical resection of the meningioma in 1984 at the age of 72 years, with complete resolution of his visual field and color defects. (He continues to thrive as of this writing at the age of 94, although he no longer plays golf!)

Meningiomas in other locations may produce seizures, abnormal gait, headache, and cranial nerve palsies.

Asymptomatic meningiomas are evaluated every 6 months. If symptoms occur, or if the tumor grows, surgical resection is indicated. Most meningiomas are removed easily if located along the meninges of the

hemispheres, but removal at the base of the brain near blood vessels and nerves is problematic.

Acoustic Neuroma

This benign tumor typically causes increasing hearing loss and mild tinnitus that gradually worsens. Patients often complain that they notice the hearing loss by not being able to use the telephone with one ear. Acoustic neuroma, also known as vestibular schwannoma, arise from vestibular nerve Schwann cells.

These tumors account for almost one tenth of all intracranial tumors. They usually occur in patients older than 20 years and are most common in 40 to 60 year olds.

Early symptoms include unilateral hearing loss and tinnitus, but as the tumor grows, difficulty with walking and ataxia occur.

On examination, a nystagmus often manifests on lateral gaze. As the brainstem becomes compromised, CN-V involvement produces hemifacial sensory loss and reduced corneal sensitivity. CN-VII involvement produces hemifacial muscle weakness.

MRI evaluation allows visualization of the tumor and the adjacent structures involved.

Surgery is performed to resect the tumor with the goal of preserving CN-VII and CN-VIII. Often hearing loss is inevitable in large tumors, because the cochlear nerve cannot be distinguished from the lesion. Because of the risks of permanent hearing loss and hemifacial sensory and motor defects, small asymptomatic acoustic neuromas, particularly in the elderly patient, may be watched with an MRI series every 6 months.

Pituitary Adenoma

This tumor composes approximately one tenth of all intracranial tumors. Most pituitary adenomas arise from the anterior portion of the pituitary gland.

These tumors can secrete hormones and the associated signs and symptoms depend on the actively secreting tumor cell type. Acromegaly occurs if the tumor secretes growth hormone. If the tumor secretes adrenocorticotropic hormone, then Cushing's disease occurs. Secreting tumors will therefore make their presence known more from their hormonal influences then from their compressional effects.

Nonsecreting pituitary adenomas produce neurologic defects because of mass effect symptoms. Although pituitary adenomas are considered benign, they may exert compressional effects on the visual pathway, cavernous sinus, and temporal lobe tip.

The hallmark visual field defect associated with a pituitary microadenoma is a bitemporal visual field defect. This defect is produced as the adenoma grows superiorly out of the sella turcica and impacts on the overlying optic chiasm. This author has documented a bitemporal hemianopsia, denser above, in a 32-year-old who complained of erectile dysfunction for a 6-month period. Neuroimaging confirmed the presence of a pituitary cyst impacting on the optic chiasm. After cyst removal through the transsphenoidal route, complete resolution of the visual field defect, and the erectile dysfunction was experienced.

In some cases hemorrhage into an undetected pituitary adenoma can occur. This causes visual loss, severe headache, and a change in mental function, and is known as pituitary apoplexy.

Pituitary tumors often respond to the medical treatments described in the text that follows.

Prolactin-Secreting Pituitary Tumor

Prolactin is a hormone that in women promotes hirsutism, galactorrhea, infertility, and amenorrhea. In men a loss of pubic hair and impotence occur. Prolactin production is suppressed by the use of bromocriptine, a dopamine agonist that also decreases tumor volume. If the tumor is unresponsive, then surgery is necessary.

Growth Hormone-Secreting Pituitary Tumor

Growth hormone promotes coarse features, acromegaly, cardiac and pulmonary disease, and spinal deformity. In addition, the hormone induces diabetes mellitus in certain individuals. Octreotide, a somatostatin analog, controls pituitary tumors that secrete growth hormone. If the tumor is unresponsive, then surgery is necessary.

Small Pituitary Tumor

If no symptomology is associated with a small, nonsecreting pituitary tumor, then no treatment is necessary, and the tumor is evaluated periodically by MRI.

Macroadenoma

Large, compressive pituitary tumors require surgical excision. The typical approach is transsphenoidal, during which the sella turcica is approached through the sphenoid sinus and nasal cavity. The tumor is dissected from the pituitary gland.

Craniopharyngioma

These tumors account for 2% of all intracranial tumors. They arise from the Rathke's pouch in the region of the third ventricle or hypothalamus. Their location is variable, but often they compress downward onto the optic chiasm and pituitary gland. In this case, the tumor typically produces bitemporal hemianopsia denser below. On CT scan these tumors have characteristic cystic changes and calcification. Treatment is surgical resection, which is difficult because of their location.

Often there is subtotal removal of the tumor, and recurrence is common.

CRANIAL NERVE CLINICOPATHOLOGIC CORRELATES

Cranial Nerve I: The Olfactory Nerve

The olfactory nerve controls the sense of smell. The inability to smell is called anosmia. Almost half of all smell disturbances are the result of sinus disease and upper respiratory infection, and one fifth of olfactory disturbances are the result of head trauma that causes damage to the cranial nerve or injury to the frontobasal cerebral cortex. Olfactory groove meningioma represents a slow-growing tumor that causes anosmia. These neoplasias have a significant morbidity, and thus early recognition of the tumor is essential.

Cranial Nerve II: The Optic Nerve

Visual field testing is mandatory in cases of optic nerve involvement. The pattern of visual field deficit may aid anatomical localization of the visual pathway lesion.

Anterior Optic Nerve

A stroke of the optic nerve at the level of the disc is known as anterior ischemic optic neuropathy (AION). The onset of the condition is heralded by a sudden, dramatic, painless loss of vision in one eye. A relative afferent papillary defect will occur on the involved side. Ophthalmoscopy will reveal a swollen, hemorrhagic, and edematous disc (disc edema). Visual field testing, even by facial confrontation, will typically reveal an altitudinal defect. Because this usually occurs on awakening, it is thought that an anatomically congested disc, combined with low blood pressure during sleep, combine to cause artery occlusion and infarct of the optic nerve. The involved eye cannot be treated, but aspirin, 81 mg/day orally, is recommended as antiplatelet therapy to reduce the chance of bilateral eye involvement.

Inflammation of the medium- to large-sized arteries of the body causes giant cell arteritis. At first there is typically a prodrome of fever, malaise, weight loss, and headaches, which may last for weeks. Patients begin to notice pain on chewing or when combing their hair because of a tender superficial temporal artery. Usually the patient seeks medical care when vision, either in one or both eyes, is lost. The condition occurs in the elderly population, usually older than 65 years. An immediate ESR should be ordered with use of the Westergren technique. Elevated sedimentation rates reach 60 to 120 mm/hr. A temporal artery biopsy will reveal giant cell granulomas. Treatment is instituted immediately with high-dose prednisone and maintained for 3 to 6 months. As the ESR drops, the systemic steroid is tapered.

Retrobulbar Optic Nerve

Optic neuritis is one of the first presenting signs of multiple sclerosis and is characterized by unilateral periocular pain that is made worse by eye movements. The term "optic neuritis" is a misnomer, however, because the condition, originally thought to be inflammatory in nature, is actually caused by demyelination. Nonetheless, the historical name persists throughout the medical literature.

Visual loss in optic neuritis is sudden, with visual field and color vision defects. The optic nerve appears normal, and so optic neuritis is often referred to as "retrobulbar optic neuritis," a condition in which "the examiner sees nothing and the patient sees nothing."

Visual recovery to a near-normal state occurs in most cases within 2 to 3 months. Eventually, pallor of the temporal optic nerve head may occur.

Treatment of optic neuritis involves the use of intravenous methylprednisolone for 3 days followed by oral prednisone in an attempt to speed visual recovery and reduce recurrent MS episodes. Oral prednisone should never be used alone in cases of optic neuritis because a greater risk of recurrence of the MS exists when compared with no treatment at all.

Cranial Nerve III: The Oculomotor Nerve

Third cranial nerve disorders are best categorized based on the anatomical location of the lesion. The nerve begins its extensive course at the Edinger-Westphal nucleus, passes through the red nucleus, enters the interpeduncular cistern, then pierces the dura en route to the cavernous sinus. From here it enters the superior orbital fissure and passes through to the orbit.

Cranial Nerve III: Palsy

Oculomotor palsy is characterized by an abducted and depressed eye with ptosis. When the lid is lifted, the involved pupil will be seen to be dilated.

CN-III: Nerve Disorders With Aneurysm

Of all patients with intracranial aneurysms, 90% are seen with CN-III palsy. The most common cause of CN-III palsy with acute headache is an aneurysm of the posterior communicating artery. In these cases pupil dilation will be present on the affected side. One third of all CN-III palsies arise from these aneurysms.

CN-III: Palsy Without Aneurysm

More than two thirds of all CN-III palsies are not the result of an aneurysm. These will present without pupillary involvement. In these cases the underlying

disorder is a systemic disease such as diabetes or systemic hypertension. The outcome is usually favorable once treatment of the underlying disorder commences, and the palsy resolves in 3 to 6 months. It is important to note that a CN-III palsy with pupil sparing does not exclude an aneurysm, but simply implies a greater chance of a benign etiology. All CN-III palsy patients are considered at risk for aneurysm and deserve a neurologic evaluation to consider the use of MRI or MRA.

Traumatic CN-III: Palsy

Traction injury to the third nerve may occur at the level of the dural entrance near the petrous bone. This injury is typical of head trauma in a car accident. Pupillary involvement mandates neuroimaging to exclude serious underlying head trauma. Recovery of traumatic CN-III palsy is characterized by aberrant regeneration, wherein axonal regrowth is misdirected and axons innervate disparate muscle groups.

Cavernous Sinus CN-III: Palsy

Cavernous sinus syndrome (CSS) is caused by slowly growing tumors within the cavernous sinus. Early symptomology includes diplopia with hemicranial facial pain along the route of the ophthalmic branch of CN-V (V2).

Orbital CN-III: Palsy

In orbital apex syndrome, a tumor or inflammatory process of the orbit causes a painful ophthalmoplegia with pupil sparing. Orbital imaging is necessary for pinpointing the etiology.

Cranial Nerve IV: The Trochlear Nerve

The patient with trochlear palsy has a hypertropia develop on the involved side. This patient has difficulty with depression of the eye because of superior oblique muscle palsy. Neuroimaging is not required in all cases of CN-IV palsy. If no other cranial nerve is involved, and the diagnosis is obvious (i.e., diabetes or trauma) then the isolated CN-IV palsy may be watched for 4 months. Typically, spontaneous improvement occurs. If other cranial nerves are involved, neuroimaging is mandatory.

Traumatic CN-IV: Nerve Palsy

Traumatic CN-IV nerve palsy is common in head trauma. These may occur in combination with a contralateral Horner's syndrome. Often, CN-IV and CN-V palsies occur simultaneously, most likely because of their positions along the lateral wall of the cavernous sinus.

Cranial Nerve V: The Trigeminal Nerve

Trigeminal Neuralgia

Brief episodes of pain within the distribution of the trigeminal nerve can be excruciating and debilitating. Also known as tic douloureux, the condition is diagnosed on the basis of history of hemifacial pains along the distribution of the trigeminal nerve. Trigeminal pain is caused by myelin loss in the posterior root of the fifth nerve. Treatment involves the use of carbamazepine which increases the threshold of neural stimulation. Other medications include phenytoin, gabapentin, and baclofen (Lioresal). If medical intervention fails, surgical decompression may be effective.

Cranial Nerve VI: The Abducens Nerve

CN-VI palsy produces an adducted eye with esotropia. Movement of the eye beyond the midline is reduced or lost altogether.

Vascular Occlusive CN-VI Palsy

Anterior inferior cerebellar artery occlusion causes extensive damage, producing nystagmus, vertigo, gaze palsy, facial paralysis, deafness, and ataxia.

Foville's Syndrome

Foville's syndrome is characterized by CN-VI nuclear palsy, facial analgesia, Horner's syndrome, and deafness.

Paramedian Basilar Artery Branch Occlusion

Infarction of the pons produces an ipsilateral gaze palsy, hemifacial paralysis, and nystagmus with limb ataxia.

Raymond's Syndrome

Raymond's syndrome is similar to other CN-VI palsies and is characterized by abduction deficit and crossed hemiplegia. If ipsilateral facial palsy is present, the condition is referred to as Millard-Gubler syndrome.

Cranial Nerve VII: The Facial Nerve

CN-VII lesions produce some of the most common cranial mononeuropathies. CN-VII has a long course, multiple functions, and four components. All lesions of the seventh cranial nerve produce some degree of facial paralysis.

Cerebral Infarct

Upper motor neuron dysfunction is characterized by facial palsy with sparing of the orbicularis oculi and frontalis muscles.

Intermedullary Pontine Lesion

Because of CN-VII and CN-VI involvement, hemifacial paralysis of the muscles of facial expression will be present, combined with an abduction deficit.

Facial Palsy

Benign idiopathic facial palsy causes loss of motor function to half of the face involving the muscles of facial expression to a variable degree. Lacrimal gland dysfunction is typical in these cases, and patients will often be seen with unilateral dry eye. A unilateral weakness will evolve during a few days. The cause of facial nerve palsy is unknown, but the condition is characterized by edema and ischemia of CN-VII within the bony canal. The condition is diagnosed on the basis of facial asymmetry with eversion of the lower lid on the involved side resulting in epiphora. Lagophthalmos is often present and responsible for an inferior corneal exposure keratitis.

When the patient attempts to close his or her eye, the involved globe is seen to pitch upwards and under the upper lid. This is known as the Bell phenomenon. Other clinical phenomenon include the inability to puff out the cheek on the involved side, the easy parting of the lids on attempted squinting, and the loss of the ability to voluntarily smile on the involved side.

The prognosis of Bell's palsy is very good, with recovery occurring in 2 weeks to 6 months. In 15% of cases, residual facial weakness or synkinesis is present. Synkinesis is the result of aberrant regeneration.

Cranial Nerve VIII: The Vestibular Nerve

CN-VIII is actually composed of two nerves: the vestibular nerve that controls equilibrium and balance, and the auditory nerve that is responsible for hearing.

Dizziness

In the United States, 8 million patients are seen each year for the complaint of dizziness. This vague complaint is responsible for more doctor visits in the patient population during a 75-year period than for any other complaint. Dizziness is best described as a feeling of light-headedness, a loss of equilibrium, vertigo, a sense of near-fainting, and a cause of unsteadiness.

Vertigo

Vertigo is the illusion of motion when the patient is completely still. The patient will report that they feel as if they are being spun around, and he or she may experience concurrent nausea, vomiting, and nystagmus. One form of vertigo, oscillopsia, is the inability to maintain stable vision during head movements, resulting in unstable visual perception. The patient literally perceives the entire visual world moving whenever head movements are initiated.

Sensorineural Hearing Loss

Sensorineural hearing loss (SNHL) occurs as the result of auditory nerve dysfunction. Hearing loss may be the result of acoustic tumors or serous otitis media. SNHL can be caused by toxic drug exposure, noise exposure, tumors, vascular disorders, and autoimmune disease.

Tinnitus

Tinnitus is an internally produced sound heard only by the patient. This noise may range from a soft ringing noise to a loud and constant roar. It is associated with exposure to loud noise, drugs, acoustic tumor, and Meniere's disease. Tinnitus may be caused by aspirin and the aminoglycosides.

CN-VIII: Central Nervous System Disorders

Inferior cerebellum infarction will cause diplopia, dysphagia, weakness, and postural instability. If the result of a hemorrhage, brain swelling and death may result. Cerebellar lesions from multiple sclerosis will cause acute vertigo and gait dysfunction similar to cerebellar infarction, but in this case the similar clinical picture does not have as ominous an etiology. Peripheral nervous system disorders likewise can cause vertigo and weakness but will not cause gait dysfunction. Neuroimaging is mandatory to distinguish between these three processes.

Peripheral Nervous System Disorders

Vertigo is caused by an acute peripheral vestibular dysfunction whereby a unilateral reduction in vestibular input compared with the contralateral and normal labyrinth input is interpreted as spinning. With unilateral vestibular loss comes the clinical sign of nystagmus. Labyrinthitis is characterized by hearing loss and tinnitus that lasts for days to weeks, and is most likely of viral etiology. Vertigo that lasts for hours and is associated with hearing loss and tinnitus is a typical sign of Meniere's disease.

Cranial Nerve IX: The Glossopharyngeal Nerve

CN-IX supplies the primary afferent pathway, and CN-X supplies the secondary afferent pathway for swallowing. Both nerves terminate in the swallowing center located in the medulla. Difficulty swallowing, or dysphagia, can occur from a host of causes.

Cranial Nerve X: The Vagus Nerve

Voice disorders can occur from tumors of the thyroid, lung, or neck. In addition, stroke, infectious diseases, and diabetes can affect voice quality, control, and pitch. Lesions of CN-X, such as are caused by high-level stroke, cause voice disorders.

Cranial Nerve XI: The Spinal Accessory Nerve

This is the major nerve input to the sternocleidomastoid muscle (SCM) and the trapezius muscle. Lesions of CN-XI cause weakness in the neck and upper back, manifested as a drooping of the shoulder. CN-XI damage occurs most frequently from surgery, carotid endarterectomy, and spinal cord lesions.

Cranial Nerve XII: The Hypoglossal Nerve

This nerve controls the final common pathway for language production and food intake. Lesions of CN-XII produce tongue deviation toward the side of the lesion. Acute carotid artery dissection causes Horner's syndrome and associated CN-XII neuropathy. Swallowing and speech are not affected unless bilateral CN-XII involvement occurs.

NEUROEYE DISEASE

The Pupil

Elegantly simple yet sensitive, the pupil examination offers a significant way to probe the neurologic pathways of the eye. Although the pupil examination requires an understanding of the neurologic anatomy of the pupil system (Box 17-1) the examiner is faced with practical questions such as "How can I differentiate a benign pupil problem from a serious one?" or "How can the pupil examination help me diagnose serious ocular or systemic disease?" This process begins by an examination of the pupil.

Examination of the Pupil

Pupil Observation

Examination of the pupil should be performed by gross observation under the magnification of a slit-lamp. The examiner should look for a round pupil that is displaced slightly nasally. Any distortion of pupil shape or misposition must be explained.

Observation of the pupil is best performed in normal, then dim, illumination. It is important to prevent the patient from feeling anxiety or fear, because this may psychologically alter pupil size.

Unequal pupil size is known as anisocoria. If anisocoria is present, then the pupil sizes should be measured. The easiest way to do this is to compare the pupil being examined to a scale on which is printed a gradient of increasing sizes of circles (Figure 17-5). This is known as the Haab scale, and it is held just temporal to the eye.

Pupil size should be measured no matter how subtle the anisocoria. These measurements should be made first in dim illumination and then in bright illumination. Looking at these measurements, the examiner should determine whether the anisocoria is greater in bright illumination or in dim light. If the anisocoria is greater in bright illumination, then the dilated pupil is usually the involved eye. If the anisocoria is greatest in dim illumination, then the eye with the constricted pupil is usually the involved eye (Figure 17-6).

When measuring pupil size, the examiner should be sure to have the patient fixate at a distant point slightly above the horizon to avoid the miosis caused by the near reflex.

The Light Reflex

The Direct Response. When a light brighter than the ambient illumination is directed into the eye, the iris will constrict, causing the pupil to reduce in size. This process is known as the pupillary light reflex.

To test the direct light reflex it is appropriate to use two hand-held illuminators such as a penlight and ophthalmoscope. The examiner should dimly illuminate both eyes by holding a light below the patient's face. The light should be just bright enough to allow the viewer to differentiate the pupil from the iris. A binocular indirect ophthalmoscope with a variable light setting can be used for this purpose. The illuminator held at such an oblique angle to the eyes will allow for only a small amount of light to enter the pupils.

The examiner should elicit the direct reflex by swinging a second bright light source upwards to shine directly into the pupil. This is a superior method to switching the bright light source on and off, because this can annoy the patient.

It is normal to note a constant amount of pupillary unrest, known as pupillary oscillations, under conditions of normal and constant illumination. These periodic fluctuations in pupil size are the result of a process whereby the iris continually adjusts the amount of light entering the eye to produce the appropriate value of retinal illumination.

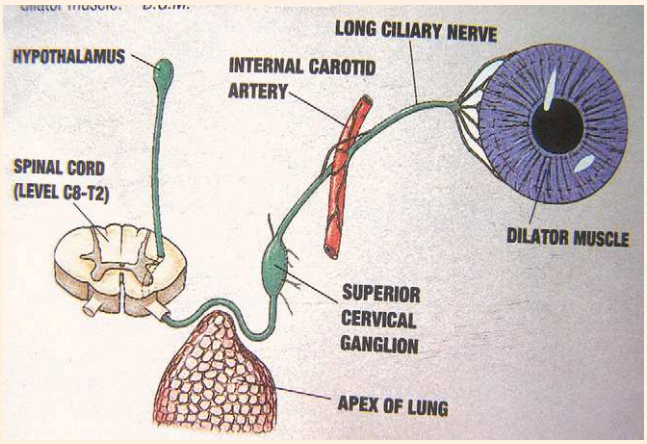
When light is directed into the eye, the pupil at first constricts vigorously and then oscillates until it stabilizes to a size larger than its initial constriction. This movement is known as the tonic pupillary reflex. The absence of this response should be noted.

The Consensual Response. The examiner should next shine a light into the same eye but observe the dimly lit, unstimulated eye. It will also constrict. This movement is known as the consensual pupillary light reflex. A loss of the consensual light reflex (Figure 17-7) means that the pupil in the unstimulated eye does not constrict.

Swinging Flashlight Test

In this test, the examiner shines a light into one pupil but off the visual axis. Both pupils will constrict because of the direct and consensual light reflex. When

BOX 17-1
PUPIL ANATOMY

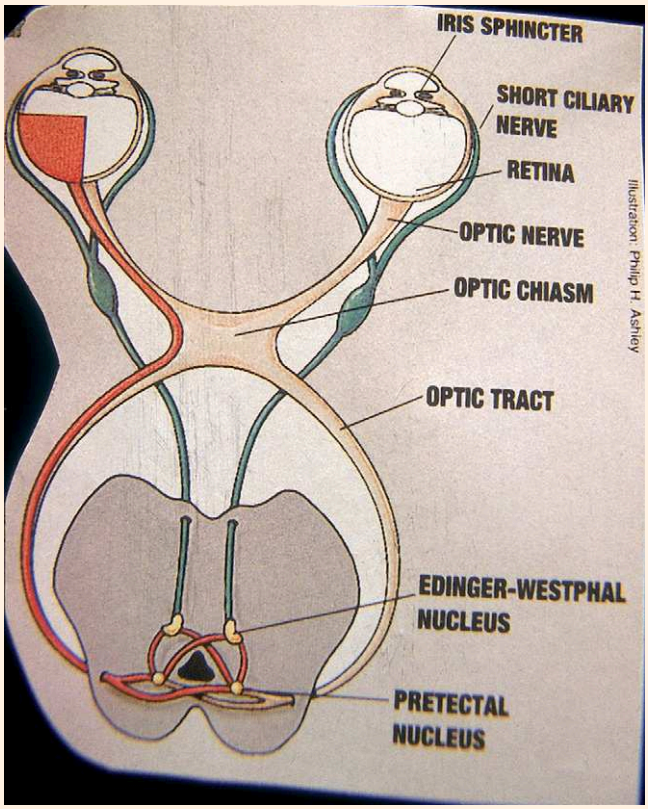


Pupil pathway anatomy. Parasympathetic innervation.

Afferent Pupillary Light Reflex Pathway
The retinal photoreceptor cells convert light quanta into chemical energy. This visual information passes through the axons of the retinal ganglion cells into the optic nerve, optic chiasm, and optic tracts. These pupillomotor fibers do partially cross in the chiasm, but do not synapse in the lateral geniculate body as the visual afferents do. Instead, they separate from the visual fibers in the posterior tract.

Midbrain Light Reflex Pathway
From the posterior optic tract, the pupillomotor fibers synapse in the pretectal nuclei. Axons of the pretectal nuclei may then either travel anterior to synapse in the ipsilateral Edinger-Westphal nucleus, or they may cross over to synapse in the contralateral pretectal nucleus. A small number of fibers cross to synapse in the contralateral Edinger-Westphal nucleus.

Efferent Pupillary Light Reflex Pathway
Preganglionic fibers are axons from the Edinger-Westphal that travel with oculomotor fibers as they exit the brainstem. The pupillomotor fibers then synapse in the ciliary ganglion. Postganglionic fibers pass to the iris through short ciliary nerves and innervate the iris sphincter. This efferent pathway represents the parasympathetic innervation of the iris.



Pupil pathway anatomy. Sympathetic nervous system.

The Sympathetic Pupillary Light Reflex
Afferent stimuli from the cortex terminate in the hypothalamus, and the hypothalamus gives rise to the first neuron of the sympathetic chain. These fibers terminate in the ciliospinal center, the second neuron arises from here to exit the spine at the thoracic trunk. The sympathetic nerves then pass close to the apical lung pleura, and terminate and synapse in the superior cervical ganglion at the base of the skull.

Postganglionic fibers emerge from this ganglion as the third neuron. These fibers travel to the carotid sinus and then enter the globe. These efferent fibers innervate the dilator of the iris.

the light is quickly moved to the other eye, both pupils will once again constrict. The examiner should be sure to have the patient gaze at a distant target and not at the light source. This test is best performed in a dimly lit room (Figure 17-8).

It is best to allow only 3 to 5 seconds of illumination on each side. The examiner should be sure not to force open the lids, because the patient's attempts to squeeze the lids shut will cause pupillary miosis.

If, when the examiner swings the light from one pupil to another, both pupils dilate instead of constricting, then the stimulated eye is conducting less electrical impulses than the unstimulated eye. These impulses are carried away from the eye by the afferent pupillary pathway (see Box 17-1 and Figure 17-9).

A relative afferent pupillary defect (RAPD) should be graded on a scale of +1 (no constriction) to +4 (brisk dilation). This scale is purely subjective. To objectively

FIGURE 17-5 ■ Pupil measurement with Haab scale.

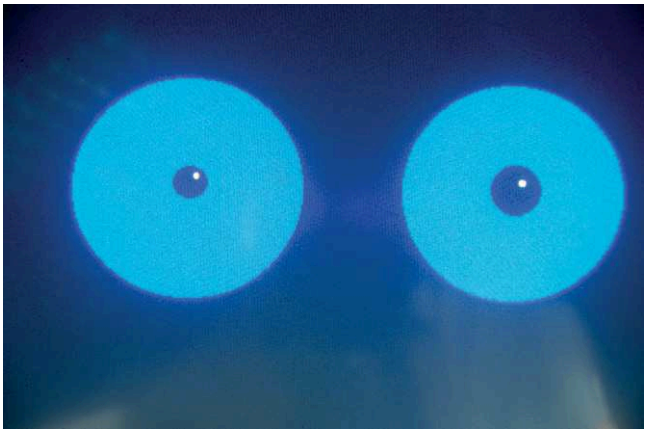


FIGURE 17-6 ■ Anisocoria greater or unequal pupil size.

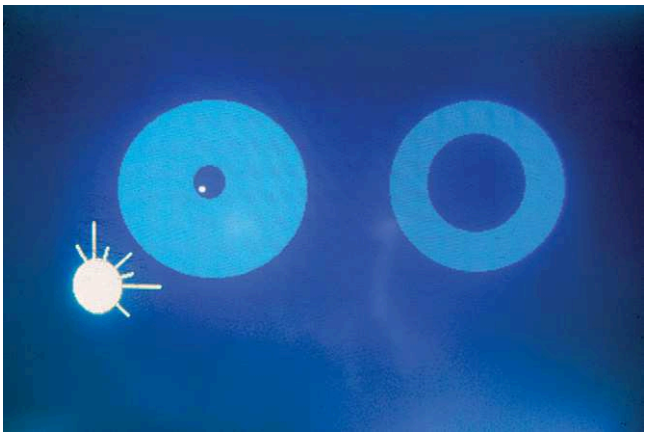


FIGURE 17-7 ■ Loss of consensual light reflex.

measure the RAPD, the examiner should hold neutral density filters in front of the uninvolved eye when performing the swinging light test. The filter density should be increased until the pupil reactions on the swing test are equal. This produces an accurate number

FIGURE 17-8 ■ Swinging light test.

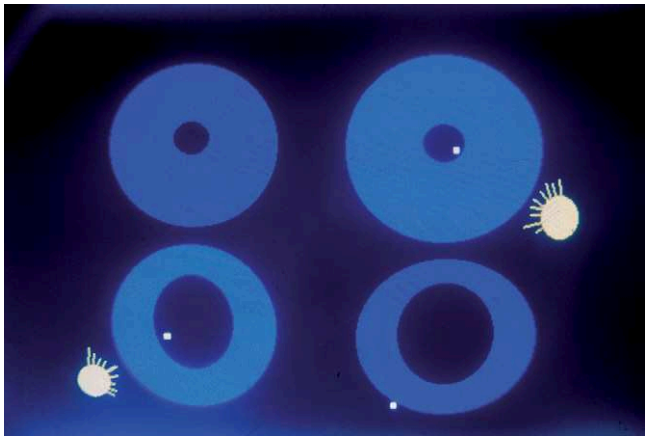


FIGURE 17-9 ■ Relative afferent pupillary defect.

in log units of the size of the RAPD, and can be used in future examinations to see whether the RAPD is changing. This reaction also demonstrates that an artificial RAPD can be created by holding a neutral density filter in front of one eye of a normal patient while performing a Swing Test. The darker filter produces less impulses carried in the afferent pathway compared with the unfiltered eye (Figure 17-10, *A* and *B*).

It is possible to confirm the presence of an RAPD when the light defect is so subtle as to be equivocal. In this case, a minimal-density neutral density filter, such as a .3 ND filter, should be used. The examiner should place the filter in front of the uninvolved eye. A swinging light test should reveal equal pupil reactions. However, when the .3 filter is placed in front of the eye suspected of having a subtle RAPD, the reduction of illumination will exaggerate the existing defect and produce a recognizable RAPD. In the normal individual, the .3 filter is not dense enough to produce an obvious artificial RAPD, or if one is produced, it will be equal in both eyes.

A

B

FIGURE 17-10 ■ **A** and **B,** Use of neutral density filters to grade an RAPD.

An RAPD is not related to visual acuity but to the threshold of light perception. Even a dense cataract that significantly reduces vision does not cause an RAPD because of light scattering, except in very rare cases.

The Near Reflex

Once the examiner has tested for the presence of a RAPD, the next step is to test the accommodative system. The patient should be asked to look at a near target while in dim (Figure 17-11) illumination. The examiner should note whether the pupil reacts by constricting. If a poor response is observed, the examiner should tap the patient on his or her own fingertip while the patient looks at it. This usually produces a fairly brisk near response. A sluggish or absent accommodative response should alert the examiner to a possible significant disorder. When the near reflex contraction is greater than the patient's best light reflex, a light-near dissociation exists and should be considered a pathology.

Next, the examiner should ask the patient to look to a distant target and assess the briskness of the pupil redilation, and note whether the dilation is prompt and brisk, or slow and delayed.

FIGURE 17-11 ■ Near response.

It is not necessary to test the near reflex when the light response is normal, but the near reflex should be tested in all cases of anisocoria.

Pupillary Cycle Times

When a focused beam of a slit-lamp is placed horizontally on the inferior iris and raised so that it just grazes the lower edge of the pupil, miosis will occur because of light entering the eye. The subsequent miosis cuts off light to the retina, causing a redilation. The pupil continues to cycle through mydriasis and miosis as long as the light is held steady on the edge of the pupil. These pupillary cycle times may be reduced in multiple sclerosis, neurosyphilis, and in RAPD. But the test is prone to errors and examiner bias, and the results have thus far been confusing

Recording Pupil Responses

Modern video cameras can be used to record pupil responses. Many of these cameras have a "gain-up" system that allows for high sensitivity in recording pupil responses even in dark irises. This author has found very favorable results using this system to record and measure pupil size and reactions.

The Abnormal Pupil

Anterior Chamber Anomalies

Congenital malformations and anomalies of the iris (Box 17-2) produce eccentric and irregular pupils. Ocular trauma that produces contusion to the globe may produce iris sphincter tears, iridodialysis and cyclodialysis that may displace the pupil and produce an irregular pupillary light reaction. Intraocular inflammation, such as anterior uveitis, may produce iris nodules and anterior and posterior synechiae, all of which may result in an inappropriate pupil shape and movement.

Finally, any abnormal pupil shape, position, or light response may be the result of the presence of an iris tumor. Any iris malformation may act as a diag-

Box 17-2
IRIS ETIOLOGIES OF PUPIL DYSFUNCTION

Iris Pathology as a Cause of Pupil Dysfunction
1. Iris coloboma: congenital absence of iris tissue.
2. Congenital aniridia: congenital absence of all of iris.
3. Persistent pupillary membrane: may cause distorted pupil responses.
4. Progressive essential iris atrophy: atrophy of iris stroma may cause ectopic pupil and distorted pupil responses.
5. Iris tumor: may distort pupil reflexes.
6. Anterior uveitis: may lead to iris nodules and synechiae, thus altering the pupil reflex.

Iris Trauma as a Cause of Pupil Dysfunction
1. Sphincter tear: may look like a coloboma.
2. Iridodialysis: tear of iris from its mooring at the root of the iris. Distorts pupil.
3. Cyclodialysis: tearing of the ciliary body away from the scleral spur, may distort the pupil.

nostic dilemma in the pupil work-up because pupil responses depend on the appropriate iris structure. The asymmetry that is characteristic of anterior chamber anomalies usually produces anisocoria.

Neurologic Anomalies: Lesion Localization—Anisocoria

The first indication that a neurologic entity may be causing a pupil problem may come with the detection of anisocoria. If this asymmetry in pupil sizes cannot be explained by physical iris changes, then the examiner must consider a neurologic cause.

In most cases of anisocoria no significant cause exists, and this is known as simple, or see-saw anisocoria. It is best seen in dim illumination and it is considered benign. Anisocoria is a significant ocular sign when it is associated with abnormal pupillary reflexes or other significant clinical signs.

Retinal, optic nerve, chiasm, and optic tract lesions do not cause anisocoria. A lesion of the intercalated neuron in the midbrain produces a transient anisocoria that is difficult to observe. Most neurologic causes of anisocoria are the result of lesions in the efferent pupillary pathway (see Box 17-1). These arise because of asymmetric disruptions of the parasympathetic or sympathetic nervous system innervation of the iris. Thus, the presence of anisocoria may help to localize a lesion to this pathway, but not its location in the pathway.

When anisocoria is greater in bright illumination, the dilated pupil is considered to be abnormal until proven otherwise. The differential diagnosis of this dilation includes a self-administered drug, a tonic pupil, or damage to the efferent fibers of the third cranial nerve because of significant and potentially catastrophic intracranial pathology.

Lesion Localization—The Relative Afferent Pupillary Defect

Neurological problems may cause pupillary problems and yet not produce anisocoria. These will usually produce an abnormal direct or consensual light reflex. Therefore, despite the absence or anisocoria, the examiner should make sure to evaluate direct and consensual pupillary responses to light stimulation.

If an abnormal result is found in this evaluation, it will most often conform to one of the following four observations.

1. A normal, brisk, direct response is seen in the tested eye, but a reduced or absent consensual response in the fellow eye. In this case, the examiner should look for abnormal iris anatomy or pharmacological blockade of the consensual iris. If none is found, the examiner should consider a neurologic problem existing in the consensual eye, most likely in the efferent pupillary pathway.
2. A reduced or absent direct pupillary response to light is seen but a brisk, rapid, consensual response of the fellow eye (Figure 17-12). Again, the examiner should exclude a pharmacological blockade of the stimulated eye or abnormal iris anatomy. If none is found, the examiner should consider a neurologic cause affecting the stimulated eye, most likely in the efferent pupillary pathway.
3. Direct stimulation of one eye results in constriction of both pupils, but stimulation of the fellow eye produces bilateral pupil dilation (Figure 17-13). This response becomes more obvious when the swinging light test is performed and will confirm the presence of a RAPD in the stimulated but poorly reacting eye. This is most likely the result of a neurologic lesion in the afferent pupillary pathway of this eye or in the contralateral optic tract.
4. You may find that both the direct and consensual responses are abolished when either eye is stimulated

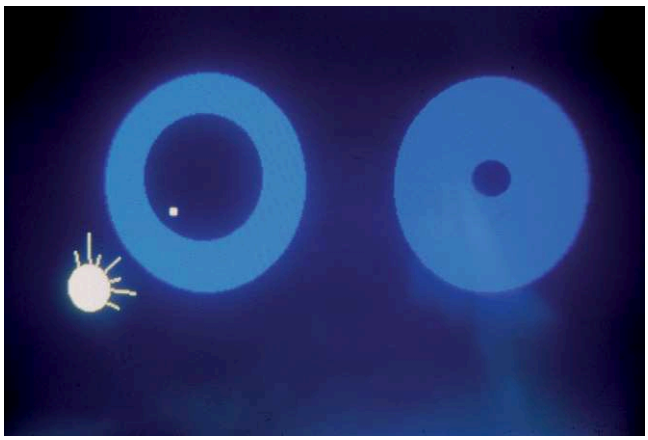


FIGURE 17-12 Negative direct response with positive consensual response.

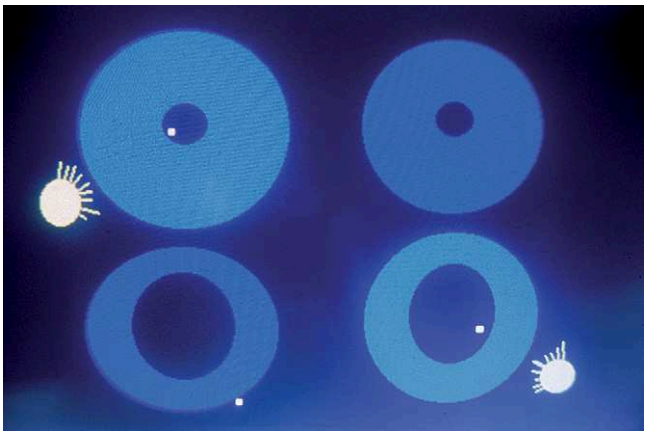


FIGURE 17-13 ■ Positive direct and consensual response but negative response in fellow eye.

(Figure 17-14). In this case, the examiner should make sure that the patient did not insert dilating or constricting drops in both eyes, causing a bilateral pharmacological blockade. If not, the examiner should use the slit-lamp to exclude iris abnormalities that may cause bilateral pupil defects. If no problems are found, then the examiner should seriously consider a neurologic lesion of the midbrain or the efferent pupillary pathways of both eyes. A bilateral afferent pupillary defect may also produce this result.

Pupillary Disturbances Caused by Neuroophthalmic Disease

Disease processes affecting the pupillary light reflexes may be classified into the following three categories, according to the anatomical location of the lesion.

1. Lesions of the afferent pupillary pathway (which carries impulses away from the retina).
2. Lesions of the midbrain (the interconnections).
3. Lesions of the efferent pupillary pathway (which carries impulses to the iris).

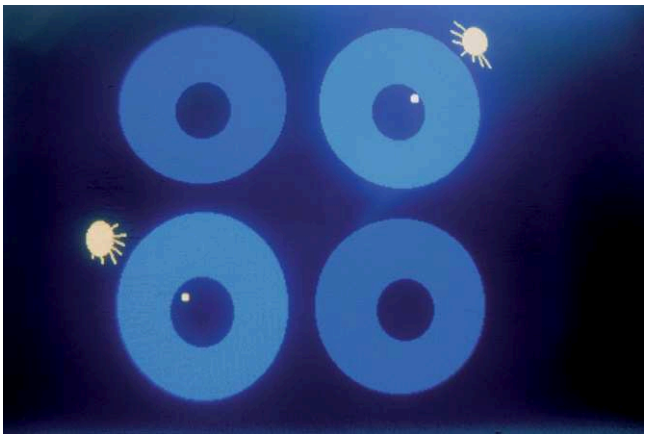


FIGURE 17-14 ■ No responses when either eye is stimulated.

Diseases of each of these three areas can cause characteristic pupillary reflexes that can aid in localization and diagnosis of the lesion.

Lesions of the Afferent Pupillary Pathway

The afferent pupillary pathway consists of the retina, optic nerve, optic chiasm and optic tract. In general, lesions of these structures are usually unilateral or asymmetric and so produce an RAPD. Lesions of the retina and optic nerve produce an ipsilateral RAPD and a complete transection of the optic tract produces a contralateral RAPD because of unequal crossing of the fibers (Table 17-3).

Retinal Disease

A retinal disease that reduces the retinal functioning of one eye more than the other will interfere with the direct light reflex of that eye. Light stimulation of the affected eye will produce a sluggish, or in the extreme case, an absent, direct reflex in the involved eye and an equally sluggish consensual response in its fellow eye. Light stimulation of the fellow intact eye produces brisk and normal response in both eyes. Significant unilateral or asymmetric retinal pathology may produce an RAPD but, as long as the efferent pupillary pathway is uninvolved, no anisocoria.

It is obvious that pupillary reflexes are not as important as ophthalmoscopy in the determination of retinal involvement, but pupillary dysfunction can serve as a clue that an in-depth evaluation of the retina is mandatory.

Optic Nerve Lesions

Just like retinal lesions, a disorder of the optic nerve causes a disturbance of only the direct light reflex; the consensual reflex (when stimulating the uninvolved eye) remains intact. A swinging light test will demonstrate a RAPD of the affected eye (Box 17-3).

When the optic nerve is completely transected (as in severe trauma), the affected pupil will be unreactive to direct light stimulation. This condition is known as amaurotic pupillary akinesia. No anisocoria is noted in optic nerve disorders as long as innervation to the iris remains intact. The degree of RAPD depends on the extent and location of the optic nerve lesion. The optic nerve lesion may produce clinical symptoms and signs that can be correlated with pupillary dysfunction in an effort to diagnose the disease (Box 17-4).

Optic Chiasm and Optic Tract Lesions

With rare exceptions, lesions of the optic chiasm and tract will not affect the pupillary responses in either eye. However, because lesions of the chiasm and tract can cause visual field defects, very discrete light stimulation of the retinal area corresponding to the visual field loss will produce a reduced pupil response when

TABLE 17-3 LESION CHARACTERISTICS BASED ON ANATOMY

LESION LOCATION	PUPILS AND RAPD	IPSILATERAL VA	VF DEFECTS	ANISOCORIA	OPTIC NERVE HEAD	NEAR REFLEX	OCULOMOTOR INVOLVEMENT	ACCOMMODATION	DISEASE OR SYNDROME
Retina	+ RAPD	Possibly reduced (Ipsilateral)	+	-	Normal	Intact	-	Reduced if ↓ VA	Varied
Optic nerve	+ RAPD	Possibly reduced (Ipsilateral)	+	-	Normal or pale	Intact	-	Intact	Varied
Optic chiasm	No RAPD unless asymmetric visual fields	Reduced	+	-	Normal or pale	Intact	-	Intact	Varied
Optic tract	Optic tract contralateral RAPD	Normal	+	-	Normal	Intact	-	Intact	Varied
Midbrain (posterior commissure)	Loss of light reaction dilated pupils	Normal	-	+	Normal	Intact	+	Reduced	Parinaud syndrome
Midbrain (sylvian aqueduct)	Miotic pupils distorted with no light responses	Normal	-	+	Normal	Intact	-	Intact	Argyll Robertson syndrome
Third nerve nucleus	Dilated ipsilateral pupil unresponsive	Normal	-	+	Normal	Absent	+	Absent	Total ophthalmoplegia
Efferent arc lesion (total lesion)	Dilated ipsilateral pupil unresponsive	Normal	-	+	Normal	Non-reactive Absent	-	Absent	Internal ophthalmoplegia
Ciliary ganglion lesion	Sluggish ipsilateral pupil (-) RAPD	Normal	-	+	Normal	Reduced	-	Reduced	Adie's tonic pupil
Sympathetic efferent system	Miosis ipsilateral (-) RAPD	Normal	-	+	Normal	Intact	-	Increased	Horner's syndrome

RAPD, Relative afferent pupillary defect; ↓, reduced visual acuity; *VA,* visual acuity.

BOX 17-3
WHAT IS A REVERSE RAPD?

A reverse RAPD is best understood by looking at an example. When a light is directed into the right pupil, both pupils constrict. Swinging the light to the left eye causes both pupils to dilate. This movement indicates a left RAPD.

But what if the left pupil cannot react because of a pharmacological blockade or abnormal left iris anatomy? If the left pupil cannot react, is it possible to detect a RAPD? Yes!

Repeat the swing test with a left RAPD and a left pupil constricted and unreactive because of the use of pilocarpine. Direct the light into the right pupil and notice that it constricts. Now swing the light to the left pupil, which does not react because of use of pilocarpine. How can you tell if a left RAPD is present if the pupil can't dilate? By looking at the right pupil as light is shined into the left eye. If the right eye dilates, this means a left RAPD is present despite the lack of left pupil response. You are looking at the opposite (or reverse) eye than in a normal swing test.

BOX 17-4
SOME OPTIC NERVE CAUSES OF RAPD

Congenital nerve anomalies
Neoplasms
Leber's optic atrophy
Temporal arteritis
Optic neuritis
Glaucoma
Multiple sclerosis
Trauma

compared with stimulation of the normal visual field area. This effect is known as pupillary hemiakinesia and is difficult to elicit because of light scattering within the eye and the inability to produce a light source discrete enough to stimulate only the affected areas. In theory, a complete transection of the optic nerve would produce a contralateral RAPD because of unequal crossing of the fibers.

Lesions of the chiasm and optic tract do not produce anisocoria unless there is damage to the pretectal decussation and nerves innervating the iris.

Upper Visual Pathway Lesions

The pupillary light reflex was long believed to be unaffected by lesions above the lateral geniculate body (see Box 17-1). Like chiasmal and optic tract lesions, however, pupillary responses will be reduced when areas of visual field loss are stimulated and compared with those areas of normal visual field sensitivity. Again, this test is difficult to perform, thus in practice upper visual pathway lesions will not produce an RAPD. Upper visual pathway lesions will not produce anisocoria.

Lesions of the Midbrain (The Interconnections)

In the pretectal area, the intercalated neurons send equal numbers of pupillomotor fibers to each side so that the two pupils constrict equally. However, anisocoria may develop from midbrain lesions when hemidecussation of fibers from the pretectal neurons to the oculomotor nuclei is interrupted. Lesions of the midbrain can produce the Argyll Robertson syndrome and Parinaud's syndrome.

Argyll Robertson Syndrome

The patient with Argyll Robertson syndrome is seen with bilateral miotic pupils. On closer examination, these miotic pupils are seen to be irregular and spastically contracted. These pupils do not react to light but constrict briskly to accommodation.

The lesion would have to be located in the midbrain and affect the interconnections between the two pretectal nuclei and two Edinger-Westphal nuclei. The lesion causes an interruption of supranuclear inhibition, thus yielding miosis. The miosis is asymmetric, and so anisocoria is almost always present.

Accommodation in Argyll Robertson syndrome remains unaffected, because accommodative fibers take a different (and thus uninvolved) pathway. Because the light reflex is absent but accommodative miosis is normal, this reaction is known as a light-near dissociation (LND) pupil. The most common cause of Argyll Robertson syndrome is neurosyphilis (Box 17-5).

Examination of the patient who is seen with Argyll Robertson pupil is best performed in dim illumination, because this will enhance the anisocoria. In addition to the near response being brisk, the redilation is also quick as compared with a tonic pupil which has a characteristic slow redilation.

Discovery of a patient with Argyll Robertson syndrome mandates a work-up for syphilis.

Midbrain Tumors

LND pupils may also occur because of midbrain tumors such as pinealomas, astrocytomas, and meningiomas. These lesions interrupt the connections between the pretectal nuclei and the Edinger-Westphal

BOX 17-5
CAUSES OF ARGYLL ROBERTSON SYNDROME

Neurosyphilis
Trauma
Tabes diabetica
Multiple sclerosis
Neoplasm
Encephalitis

nuclei. Unlike the Argyll Robertson syndrome, however, these lesions produce bilateral oval mydriasis with anisocoria.

Pineal tumors can cause bilateral dilated pupils that are unresponsive to light and are accompanied by a vertical gaze palsy, accommodative weakness, and nystagmus on attempted upward gaze. This constellation of clinical signs is known as Parinaud's syndrome.

Lesions of the Efferent Pupillary Pathway

The characteristic sign of an efferent pathway defect is anisocoria. Efferent pupillary pathway problems may result from lesions of the parasympathetic pupillary fibers or interruption of the sympathetic pathway.

Parasympathetic Pupillary Fiber Lesions

These lesions are differentiated on the basis of whether the lesion affects the parasympathetic (constricting) impulses at the oculomotor nerve nucleus (preganglionic, or first neuron) or further on at the ciliary ganglion nucleus (postganglionic, or second neuron). In either case, both pupillary light reflex and accommodation are impaired.

Efferent Third-Nerve Deficits

Complete third-nerve palsy will result in total ophthalmoplegia with the characteristic signs of an eye that is "down-and-out," with complete unilateral ptosis and a fixed, dilated pupil. Paralysis of the superior rectus, inferior rectus, medial rectus, and inferior oblique muscles is present, with loss of adduction and superior and inferior gaze. Accommodation is also lost, as well as the near light reflex.

The dilated pupil is fixed, despite light stimulation of the fellow eye. This sign differentiates this pupil from pretectal involvement, which reduces the consensual reflex alone and not the direct response.

A fixed, dilated pupil should always be considered a sign of significant and catastrophic disease such as tumor, aneurysm, infection, and intracranial hemorrhage. The examiner should look for associated neurologic signs, but if inadvertent pharmacological installation or a mydriatic is suspected, he or she should confirm it by instilling 0.1% pilocarpine and then 1% pilocarpine drops in the eye. Dilute pilocarpine will not constrict a pharmacologically blocked pupil.

Sites of Third-Nerve Damage

Nuclear Lesions

Because the Edinger-Westphal nuclei are so close together, these rare deficits are usually bilateral with involvement of all extraocular muscles and loss of accommodation. The causes of nuclear third-nerve lesions include tumors, infections, multiple sclerosis, and vascular accidents.

Fascicular Lesions

The fibers from the nucleus to the interpeduncular fossa are spread out so the effects are usually partial with pupil effects associated with contralateral hemiplegias or ataxias.

Basal Lesions

Third-nerve damage close to its emergence from the brainstem causes a partial oculomotor deficit with pupil dilation and may result from subarachnoid hemorrhage. For this reason, a dilated pupil is of grave concern.

Cavernous Sinus

Tumor, infection, inflammation, or intracavernous aneurysm may cause involvement of cranial nerves III, IV, V, and VI, as well as the sympathetic pupillomotor fibers. This causes a pupil that is smaller in darkness (because of loss of the sympathetic fibers) and larger in bright light (because of loss of the third nerve). Associated pain and anesthesia of the face are present.

Orbital Third-Nerve Lesions

Trauma, tumor, aneurysm and infection from a tooth abscess can cause vision loss, RAPD (if the afferents are involved), parasympathetic, and sympathetic involvement.

The Tonic Pupil

Postganglionic, or second-neuron, lesions occur anywhere from the ciliary ganglion to the eye. A lesion affecting these parasympathetic fibers causes anisocoria with a larger pupil that reacts poorly to both light and accommodative effort. This condition is known as a tonic pupil. It is more obvious in bright illumination, because in dim illumination both pupils may appear to be equally dilated. The tonic pupil may demonstrate a distorted pupil shape and a bizarre, irregular, and slow contraction and redilation to light stimulus.

The lesion that causes this pupil is most likely located in the ciliary ganglion, which causes the eye to be hypersensitive to dilute cholinergic agents (Table 17-4). When a tonic pupil is of unknown cause, it is termed an Adie's syndrome. It may be accompanied by loss of the deep tendon knee reflexes. Serologic testing should be performed to exclude syphilis in cases of Adie's tonic pupil (see *Case Report: A Case of Bilateral Adie's Tonic Pupil* in this chapter).

In the tonic pupil the ciliary ganglion is damaged, usually because of an obscure etiology. Most of the neurons die, causing a loss of accommodation and pupil dilation. The surviving neurons send new axon sprouts to the eye. This reinnervation is diffuse, and irregular link-ups cause wormlike contractions of the pupil known as vermiform (wormlike) movements.

TABLE 17-4 DIAGNOSTIC PUPIL PHARMACOLOGY

AGENT	CLASSIFICATION	ACTION	USE
Cocaine 4%	Sympathomimetic	Mydriatic	Fails to dilate pupil in Horner's syndrome
Paredrine 1%	Sympathomimetic	Mydriatic	Dilates preganglionic pupil but not postganglionic pupil in Horner's syndrome
Pilocarpine Dilute: 1/12% or 1/16%	Parasympathomimetic	No constriction	Will constrict an Adie's tonic pupil due to hypersensitivity
Pilocarpine 1%	Parasympathomimetic	Miosis	Will fail to constrict a pharmacologically dilated pupil

If pain is associated with a tonic pupil, then the patient should be tested for an intracranial lesion or orbital mass. Dilute pilocarpine, 1/16% will constrict a tonic pupil but not a normal pupil.

Sympathetic Pupillary Fiber Lesions

A lesion of the sympathetic innervation to the iris dilator produces a miotic pupil. In addition, loss of sympathetic innervation to the upper lid produces a ptosis. This combination of ptosis and miosis is characteristic of Horner's syndrome. The unilateral miosis produces anisocoria, which will be greatest in dim illumination, because bright light will make both pupils appear constricted. No loss of accommodation is present. There are numerous causative processes of Horner's syndrome (Box 17-6).

To determine the etiology of Horner's syndrome the examiner must first determine the location of the lesion. Interruption of the sympathetic pathway to the iris may occur between the hypothalamus and spinal cord (central, or first neuron), between the spinal cord and superior cervical ganglion (second neuron), and between the superior cervical ganglion and the iris (third neuron).

First- and second-neuron Horner's syndromes are considered preganglionic, and third-neuron Horner's syndrome is postganglionic.

Differentiating preganglionic from a postganglionic Horner's syndrome begins with the determination of sweat pattern distribution. Brainstem (first neuron) lesions cause ipsilateral loss of sweat to the face and body (anhidrosis). Sympathetic disruption in the spinal cord produces anhidrosis of half the face and neck. Second neuron involvement produces anhidrosis of the face. Postganglionic fiber disruption in the neck, the base of the skull, and orbit produces anhidrosis of only the forehead.

BOX 17-6
PERIPHERAL CAUSES OF HORNER'S SYNDROME

Neck trauma
Goiter
Neck surgery
Internal carotid artery
Aneurysm
History of incubation for surgery
Cluster headache
Apical pulmonary tumor
Neoplasms

Drug Responses In Horner's Syndrome

Pharmacological confirmation of a Horner's syndrome may be accomplished by the instillation of 4% cocaine drops in the eye. Cocaine will cause mydriasis in the normal eye but fail to dilate the affected eye. (However, in first-neuron Horner's syndrome, mild mydriasis may occur.) Thus, cocaine can confirm a sympathetic disruption but not localize it.

Because cocaine cannot differentiate preganglionic from postganglionic involvement, Paredrine 1% may be used to isolate the location of the lesion. Paredrine 1% dilates a preganglionic pupil normally but will not dilate a Horner's syndrome pupil that is the result of postganglionic damage.

Causes of Horner's Syndrome

Of preganglionic lesions, 50% are malignant in nature and many of the remaining are caused by vehicular "whiplash" injury. Interruption of the preganglionic sympathetic pathway of the second neuron may be the result of a tumor, and an apical pulmonary carcinoma should be excluded.

Most postganglionic (third-neuron) Horner's syndromes are vascular in nature and many of these patients experience "cluster" headaches (see Box 17-6).

Case Report: A Case of Bilateral Adie's Tonic Pupil

A 48-year-old white male was seen in our clinic with a complaint of unilateral sudden-onset loss of near accommodation. He had visual acuities of 20/20 in both eyes but loss of accommodation at near in his right eye, with minimal accommodation reduction in his left eye. Anisocoria was present, with his right pupil being larger than his left, and the anisocoria more apparent

in bright illumination. Slit-lamp evaluation demonstrated the right pupil to constrict sluggishly and segmentally to bright light. Consensual response in the fellow eye was normal. The near reflex was much reduced in the right eye. No RAPD was present. Our impression was unilateral Adie's tonic pupil. The patient was asked to return for pharmacological testing to confirm tonic pupil.

On his return the anisocoria (Figure 17-15) was still present, but both pupils were now sluggish to light and accommodation. Very dilute pilocarpine was applied to both eyes, which caused miosis (Figure 17-16), thereby verifying a bilateral Adie's tonic pupil. There was a loss of deep tendon knee reflexes on both sides. Serological testing was negative for syphilis.

Case Report: A Case of Inadvertent Mydriatic Instillation (Pharmacological Blockade, or, How Knowing a Little Too Much Can Hurt)

A 32-year-old nurse was seen in our clinic in a near panic because of a unilateral dilated pupil. She denied any history of trauma and denied instillation of eye drops. Visual acuities, confrontation fields, extraocular muscle motilities, and external and internal examination were normal. Direct light stimulation of the involved eye failed to produce any constriction but did result in normal miosis of the consensual eye.

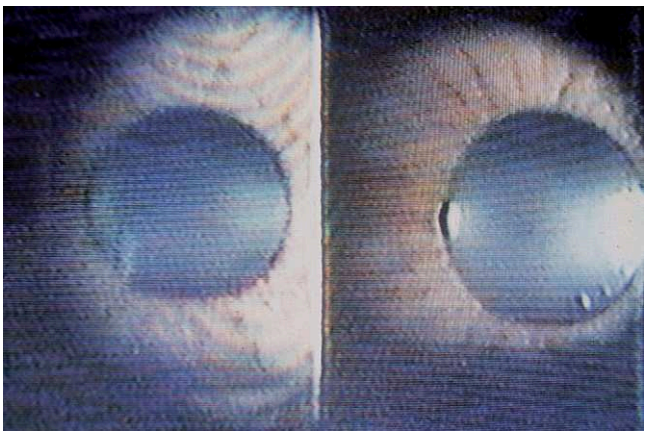


FIGURE 17-15 ■ Adie's tonic pupil: anisocoria. Case report.

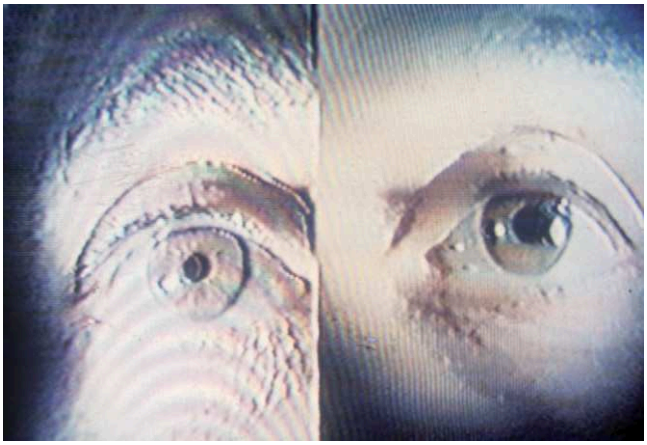


FIGURE 17-16 ■ Adie's tonic pupil: dilute pilocarpine test. Case report.

Because the day of her visit was a Monday, I asked her what she had done over the weekend. She replied that she had gone sailing. Asked whether she had gotten seasick, she replied she hadn't because she wore a transdermal patch to prevent seasickness (bingo!).

The patch contains scopolamine, which is a potent dilator. At some point she had touched her eye and caused dilation of the pupil. One drop of 1/12% pilocarpine was instilled in the eye and failed to constrict the pupil, so no hypersensitivity was present. Pilocarpine 1% also failed to constrict the pupil, thus confirming a pharmacological blockade.

This case demonstrates that history is as significant as any pupil testing in determination of etiology of a pupil dysfunction.

Ocular Motility Dysfunction

The refinement of binocular vision has been a critical development in the course of human evolution. The ability to place an image of interest on both foveas simultaneously and in all positions of gaze must occur in spite of head movement or object motion. Without a means to counteract even the subtlest of head movements, images would sweep across the retina, causing degradation of visual acuity. Even the tiniest of head vibrations because of cardiac pulsation would blur vision if no compensatory mechanism were present.

This chapter is divided into two sections. The first part deals with the supranuclear motility system, its anatomy, examination, and disease processes. The second section reviews the infranuclear motility system, which comprises eye movements generated by the third, fourth, and sixth cranial nerves.

The Supranuclear Motility System

Four general classes of eye movements are known as supranuclear ocular motility systems. These movements stabilize retinal images and are defined by the specific stimulus needed to initiate the given movement, and a description of the type of movement elicited.

The first of these eye movements, the smooth pursuit system, acts to hold the image of a moving target on the fovea. Another one, the saccadic system, directs both foveas toward the image of regard. The vestibular-optokinetic movements act to hold the images of the visualized world steady on the retina during head rotation. Finally, the vergence system acts to move the eyes in opposite directions so that images of a single object in space are placed simultaneously on the fovea.

These complex supranuclear eye movements take the coordinated efforts of whole muscle groups. No one

muscle is involved and so disorders of the supranuclear system cause a loss of one or more of these gaze functions, rarely producing the complaint of diplopia.

When a patient experiences two different images that seem to occupy the same location in space, he or she may complain of "double vision." It must not be assumed, however, that these complaints of diplopia always represent a misalignment of the eyes. For example, a patient with monocular diplopia may have normal eye posture. Furthermore, because a patient may suppress the vision in the nonfixating eye, the lack of a diplopic complaint in no way negates the presence of strabismus.

Misalignment of the two visual axes with diplopia may occur in rare cases because of disorders of the supranuclear, internuclear, or nuclear areas for cranial nerves III, IV, and VI. More often, ocular misalignment is the result of disease processes in the infranuclear structures, including the fascicle, the nerve, the myoneural junction, or the extraocular muscles, and this will be discussed later in this chapter.

The supranuclear gaze centers are responsible for the eye movements involving vestibular, optokinetic, saccadic, smooth pursuit, and vergence systems. Each of these will be discussed and their anatomical substrates described. The significant pathological processes that commonly affect each system will be presented, along with the relevant differential diagnosis and treatment modalities.

The Pursuit System

This system allows for smooth, slow (40 degrees per second) eye movement, which enables the viewer to track targets by keeping the image of regard on the fovea. This response is stimulated by movement of an image on the retina, usually near the fovea. The anatomical substrate for the pursuit system is found in the occipitoparietal junction.

Neural Pathway of the Pursuit System

Cortical control of the smooth pursuit system arises from the parieto-occipito-temporal junction (POT) and is known as the parieto-occipito-temporal-mesencephalic pathway. Ipsilateral control of the pathway exists, so that the left POT controls smooth pursuits to the left, and the right POT controls smooth pursuits to the right. It should be stated that the exact neural pathway is not yet known, although the signal to begin a pursuit movement begins in the paramedian pontine reticular formation (Figure 17-17).

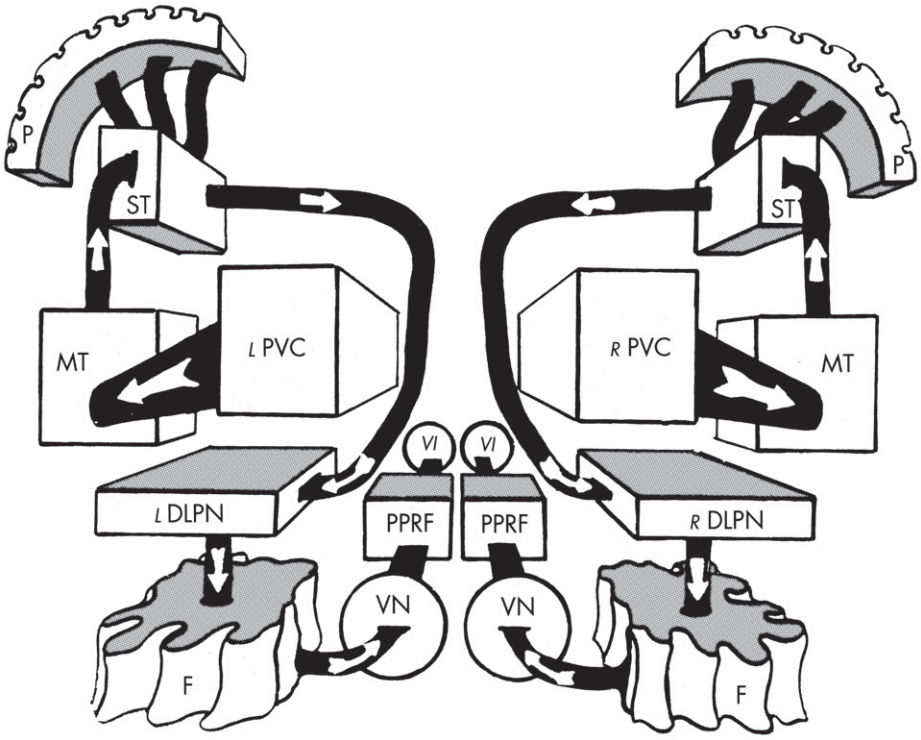


FIGURE 17-17 ■ Pursuit pathway. *RPVC,* Right posterior visual cortex; *LPVC,* left visual cortex; *MT,* middle temporal visual area; *ST,* medial superior temporal visual area; *RDLPN,* right dorsolateral pontine nuclei; *F,* flocculus; *VN,* vestibular nuclei; *PPRF,* paramedian pontine nuclei; *VI,* sixth-nerve nuclei. (From Blaustein BH, ed: *Ocular manifestations of neurologic disease,* St Louis, 1996, Mosby. Illustration by B. Muchnick.)

Clinical Examination of the Pursuit System

The patient with smooth pursuit disorders rarely has visual complaints, because he or she can use a series of saccades to track moving objects.

The examiner should test the patients by having them keep their heads still while tracking a slowly moving target with their eyes. An optokinetic nystagmus flag may be passed in front of the patients to elicit pursuit movements (slow phases of the nystagmus).

The abnormal pursuit movement will be replaced by a series of saccades while the patients follow the target.

Pursuit Disorders

Disorders of the smooth pursuit system are caused by lesions in the occipitoparietal junction, the parapontine reticular formation (PPRF) (although the PPRF is not a major part of the pursuit pathway), and the brainstem. The disorders are typified by a series of small saccades that replace the long pursuit movement. This process may be the result of disorders of the cerebellum, such as MS, aging, medications (e.g., tranquilizers), and progressive supranuclear palsy.

It is important to realize that lesions of the optic tract, temporal lobe, or occipital lobe that produce a homonomous hemianopsia will not usually affect the smooth pursuit system. A deep posterior hemispheric lesion with hemianopsia, however, will produce an abnormal pursuit away from the hemianopsia.

Disorders of the pursuit system are divided into unilateral and bilateral dysfunction. Unilateral pursuit paresis, as described above, arises from deep occipital lesions, causing a hemianopsia and a "saccadic" pursuit in the direction of the lesion. Bilateral dysfunction manifests itself as a reduction in pursuit velocity when a patient attempts to follow a target. A number of small saccades replace the one long pursuit movement, and may result from sedative drug use, fatigue, or cerebral, cerebellar, and brainstem disease.

The Saccadic System

These most rapid of eye movements (500 degrees per second) allow the visual system to move to accurately pinpoint the image of an object on the fovea.

The quick phases of vestibular nystagmus are considered saccades, as are involuntary and voluntary fixation changes.

Saccadic movements may be stimulated by conscious command of the observer toward a visual or auditory point of interest, or by unconscious random eye movements or rapid eye movement sleep.

Anatomically, nonfoveal saccadic initiation most likely begins in the contralateral frontal eye fields (specifically Brodmann's area 8) and superior colliculi, and foveal saccades are initiated at the occipitoparietal junction. The major pathway of the saccadic projections arrives at the PPRF at the level of the abducens nucleus. The PPRF is responsible for conjugate ipsilateral horizontal gaze movements. Vertical saccadic movements require bilateral cortical mediation.

The Neural Pathway of the Saccadic System

Horizontal saccades begin in the contralateral frontal lobe. The descending, polysynaptic saccadic fibers decussate at the midbrain-pontine junction and terminate in the contralateral PPRF (Figure 17-18).

The reticular formation in the pons generates saccades of all types by inputs to the ocular motor nuclei. Stimulation of the left Brodmann's area 8 causes a conjugate saccade to the right, and stimulation of the right Brodmann's area 8 causes movement to the left.

Clinical Examination of Saccadic Disorders

To clinically evaluate saccadic eye movements, the examiner should have the patient alternate the gaze between two objects, both horizontally and vertically in all positions of gaze. Any saccadic slowing, lack of accuracy, lag of initiation, and inappropriate saccades

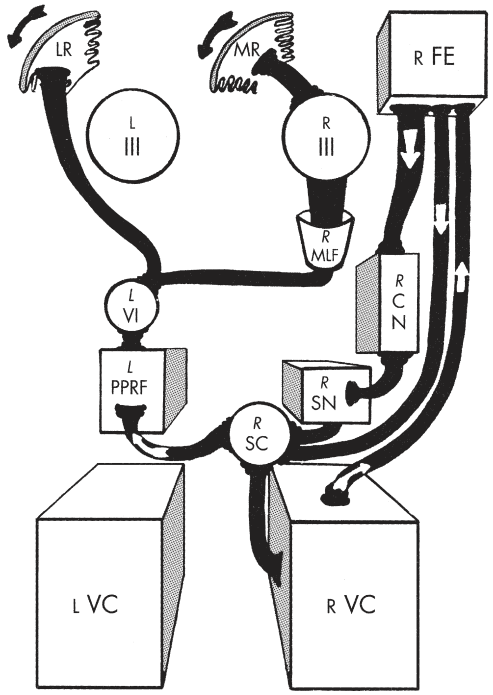


FIGURE 17-18 ■ Saccadic pathway. *RVC,* Right visual cortex; *LVC,* left visual cortex; *RFE,* right frontal eyefield; *RCN,* right caudate nucleus; *RSN,* right substantial nigra; *RSC,* right superior colliculus; *LPPRF,* left paramedian pontine reticular formation; *LV I,* left sixth-nerve nuclei; *RMLF,* right medial longitudinal fasciculus; *R III,* right third-nerve nucleus; *L III,* left third-nerve nucleus; *MR,* right medial rectus; *LR,* left lateral rectus. (From Blaustein BH, ed: *Ocular manifestations of neurologic disease,* St Louis, 1996, Mosby. Illustration by B. Muchnick.)

should be noted. Saccadic slowing can best be demonstrated by having the patient fixate between two widely spaced targets. Any saccadic lag should be noted by timing the initiating of the saccade.

If a saccadic disorder is noted, then further neurologic evaluation is needed to localize the lesion based on the anatomical organization of the saccadic system.

Saccadic Disorders

Disorders that affect saccades may be classified by their effect on saccadic characteristics. Thus, we see pathology of saccadic speed, accuracy, initiation, and inappropriateness.

Slow saccades occur in patients with extraocular muscle dysfunction, ocular motor nerve paresis, or medial longitudinal fasciculus (MLF) lesions, causing INO. INO is characterized by slow saccadic adduction (see section on horizontal gaze palsies in this chapter).

Central neurologic disorders causing slow saccadic movements include Huntington's chorea, lipid storage disorders, and progressive supranuclear palsy. In addition, slow saccades are expected in sleepy, intoxicated, or elderly patients.

Huntington's chorea is an autosomally dominant genetic disease with slow onset in the late thirties. The face and distal extremities demonstrate inappropriate movements. Mental deterioration eventually leads to dementia. The early eye sign is a loss of saccadic velocity. Saccades are often slow, particularly in the vertical direction, most likely because of lesions in the MLF.

Inaccurate saccades are primarily caused by cerebellar disease, although they can occur in patients with brainstem disorders and visual field hemianopsias.

Inappropriate saccades that interfere with vision may be caused by MS, cerebellar disease, Huntington's chorea, and progressive supranuclear palsy.

Supranuclear palsy is a degeneration of the central nervous system in elderly patients. The first sign is loss of downgaze with immobility of the neck, followed by loss of upgaze, then horizontal gaze and, finally, pursuits. Loss of facial expression and dementia are inevitable, and death usually will occur within a decade of onset. The first eye movement to be affected is downward gaze, with horizontal and upward eye movements lost later in the course of the disease. Saccades become slowed and are of reduced size, and all movements eventually are extinguished. The administering of dopaminergic drugs helps locomotion but not eye movements.

Like pursuit disorders, saccadic disorders can be caused by unilateral or bilateral lesions. An acute, unilateral frontal lesion with preservation of the contralateral hemisphere usually produces a transient saccadic palsy, which improves and eventually resolves with time. This palsy occurs in rare cases with a chronic process such as neoplasm. The pursuit system is not affected.

Bilateral frontal lesions cause saccadic paresis in both directions. Again, the pursuit system is unaffected. Oculomotor apraxia, or the inability to initiate normal horizontal saccades occurs because of such bilateral frontal lesions. Delayed initiation of saccades may be observed in elderly, inattentive, and intoxicated patients. If it occurs in the alert patient, it causes ocular motor apraxia, and may be the result of bilateral parietal lobe lesions. Another cause of delayed saccadic initiation is Parkinson's disease.

Parkinson's disease is a degeneration of the extrapyramidal system and may cause a loss of upward gaze, followed by downward gaze and, finally, horizontal eye movements. Convergence may fail, producing diplopia at near. Involuntary head motions and drooling may occur. The disease is characterized by tremor, muscular rigidity, and progressive supranuclear palsy with decreased convergence, superior gaze immobility, and saccadic initiation delays.

The Vestibular-Optokinetic System

The vestibuloocular reflex acts to steady retinal images during head movement. This reflex is driven by sensory cells within the semicircular canals, which detect motion, whether the result of gravity or acceleration, in their given plane.

The vestibuloocular reflex produces eye movements that are equal and opposite to quick, short-lived head motions. The optokinetic system stabilizes the image during a prolonged rotation of the head (such as an ice-skater spinning for 30 seconds).

The Neural Pathway of the Vestibular-Optokinetic System

The semicircular canals are stimulated by transient head motion, which causes mechanical shearing effects on specialized hair cells within the canals. These cells transduce endolymph movement into neural impulses that are sent to the contralateral horizontal gaze center. Information sent from the right semicircular canal travels to the left horizontal gaze center, resulting in slow eye movement to the left. The optokinetic neural pathway is as yet unknown (Figure 17-19).

Clinical Examination of Vestibular Disease

When examining a patient with complaints of dizziness, vertigo, or imbalance, the clinician must consider vestibular disease. A patient who reports a sensation of rotation of one side may have peripheral vestibular disease affecting the opposite side. On examination, the slow phase of the nystagmus will be away from the affected side.

To examine for vestibular imbalance, the optometrist should hold the patient's head still and have them fixate a distant target. Any nystagmus-type movements should be noted. Small movements may be discerned

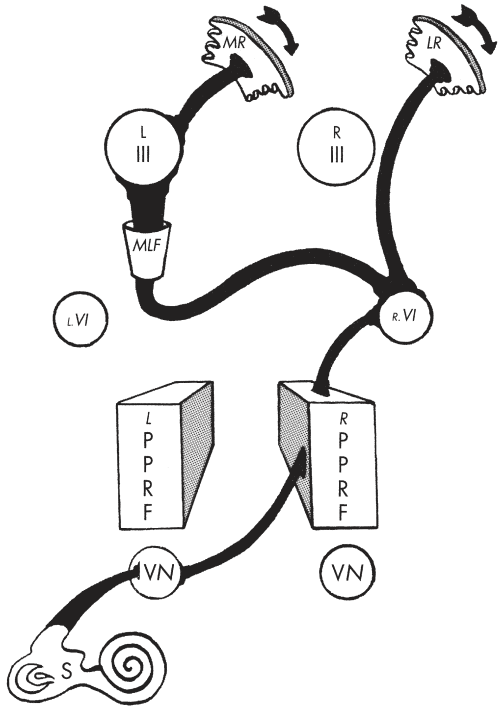


FIGURE 17-19 ■ Neural pathway for vestibular eye movements: vestibular and cochlear testing. *S,* Right semicircular canal; *VN,* vestibular nuclei; *RPPRF,* right paramedian pontine reticular formation; *LPPRF,* left paramedian pontine reticular formation; *R VI,* right sixth-nerve nuclei; *L VI,* left sixth-nerve nuclei; *MLF,* medial longitudinal fasciculus; *R III,* right third-nerve nuclei; *L III,* left third-nerve nuclei; *LR,* right lateral rectus muscle; *MR,* left medial rectus muscle. (From Blaustein BH: *Ocular manifestations of neurologic disease,* St Louis, 1996, Mosby. Illustration by B. Muchnick.)

by using ophthalmoscopy to visualize a retinal structure (e.g., the nerve head) minutely quivering.

Vestibular nystagmus is accentuated when fixation is removed, so the patient may be fogged with high plus lenses in a trial frame. If nystagmus is still not noted, the examiner should have the patient shake his or her head horizontally for 10 seconds and then stop. The examiner should look for a residual jerk nystagmus, and then repeat this test in the vertical plane.

Finally, caloric testing can adequately evaluate the integrity of the labyrinthine apparatus. To test the horizontal canal, the patient is placed in a supine position with the head raised 30 degrees. This angle places the horizontal canal in a vertical position. Introduction of cold water into the external auditory canal produces convection currents in the endolymph, which causes a jerk nystagmus, the fast phase of which is opposite the ear tested. If warm water is introduced, then the fast component is toward the same ear being tested. To remember this test, use the mnemonic COWS, which stands for cold, opposite, warm, same (see Figure 17-19).

Vestibular Disease

Vestibular disease causes a "sawtooth" nystagmus, characterized by slow-phase drifts of constant velocity with corrective quick phases.

Peripheral vestibular disease should be differentiated from central lesions. Peripheral disease that affects primarily the labyrinthine apparatus generally causes an acute sensation of severe vertigo and deafness. This condition is usually caused by toxic reactions, infections, and inflammatory processes.

Central vestibular disease usually presents with chronic mild vertigo with no deafness, and is usually the result of ischemia, acoustic neuroma, or demyelinating disease.

Unilateral peripheral disorders of the vestibular system typically produce nystagmus because of differences in the neural activity between the left and right vestibular nuclei. Recovery usually occurs unless some destruction of a single canal has occurred that causes residual permanent nystagmus.

A bilateral peripheral vestibular loss of semicircular function causes image movement across the retina with every head movement. Eventually, the patient will adapt to this condition.

Wallenberg's Syndrome and the Vestibular System

Wallenberg's syndrome is caused by a lateral medullary infarction secondary to an occlusion of the posterior, inferior cerebellar artery, causing a disorder of the central vestibular connections. The patient will exhibit nystagmus, with the slow-phase toward the side of the lesion. Ipsilateral loss of pain and temperature sensation will also be present. A loss of pain and temperature sensation also will occur in the contralateral body and limbs. An ipsilateral Horner's syndrome may be noted. These clinical signs and symptoms will vary greatly, depending on the amount of brainstem and cerebellar damage.

The Vergence System

When a viewed object changes its distance from the observer, disparate retinal images stimulate the vergence system to either diverge or converge to reestablish bifoveal vision. This system, unlike the others, causes the eyes to move in opposite directions. The higher supranuclear pathways responsible for convergence and divergence remain largely unknown, although we know that convergence motor cells are located in the midbrain reticular formation dorsal to the oculomotor nucleus.

Two stimuli cause the vergence response. One is the disparity of the two retinal images, and causes a fusional vergence movement. The other stimulus is the retinal blur that occurs when an object changes its distance to the observer. This stimulus causes an accommodative

vergence response, as part of the near triad with lens accommodation and pupil miosis.

Vergence Disorders

Disorders affecting the vergence system may best be divided into congenital and acquired defects of either convergence or divergence. Although the symptom of diplopia is rare in the other classes of eye movements, it is often reported in cases of divergence or convergence paralysis.

Clinical Examination of Vergence Disorders

The examiner must first determine whether the presenting strabismus is an inborn defect (which is usually the result of systemically benign, visual system "miswiring," or a lack of cortical fusional ability), or an acquired defect with significant neurologic implications. This question is not an uncommon diagnostic dilemma.

First, a complete history is essential. If the patient reports a childhood history of "squint" or "crossed eyes," then, unless additional significant neurologic signs and symptoms are present, the history has settled the issue. Typically, a lack of diplopia in these cases is the result of suppression or amblyopia. In this case the patient may report a "lazy eye," which possibly was treated with patching therapy as an infant.

Uncommonly, a case of anomalous retinal correspondence may be uncovered, which also permits vision without diplopia. In this case, a peripheral retinal area of the strabismic eye somehow acquires an anomalous common direction with the fovea of the fixating eye. This condition is clearly a sensory adaptation to chronic strabismus.

If the history fails to settle the matter, then an examination is crucial to rule out significant neurologic disease and to confirm long-standing strabismus.

The ocular misalignment must be measured in all positions of gaze. If the amount of deviation is equal in all positions of gaze no matter which eye is fixating, then this is a strabismus of long standing, because the ocular system has had a long time to adjust to the misalignment of the eyes. This condition is termed a concomitant strabismus, which is nonparetic in nature and rarely has significant neurologic ramifications. By far the most common cause of concomitant deviations is childhood strabismus, which is usually congenital but may be acquired, as in cases of vergence paresis and skew deviation.

Many patients are found to have benign concomitant phorias when tested with the alternate-cover or prism tests. These phorias usually present no significant disturbance to the visual system, although some have proposed that these small deviations may be responsible for headaches, asthenopia, and reading complaints.

True concomitant strabismus exists if the fusional mechanism of the visual system cannot overcome the amount of deviation. Nonparalytic strabismus may be the result of orbital disease, refractive error, or error of accommodative-convergence synkinesis.

If childhood strabismus is not determined by history, but is still suspected, it may be helpful to find amblyopia of long standing. Also, the presence of large fusional amplitudes points to childhood deviation, particularly if a decompensating phoria in an adult is suspected.

If childhood strabismus is ruled out, then acquired concomitant deviation, including vergence paresis or skew deviation, should be considered.

Vergence Paresis

Vergence paresis, an acquired form of concomitant deviation, includes both divergence and convergence paresis. Unlike childhood strabismus, divergence and convergence paralysis causes symptoms of diplopia.

In divergence paralysis, a supranuclear paresis causes esotropia that is equal in all positions of gaze. Although simulating a mild bilateral sixth-nerve palsy, divergence paralysis is considered by most to be a separate entity from sixth-nerve palsies and divergence insufficiencies. If no other signs are present, then no other testing need be performed. The condition tends to be benign and self-limiting. Its causes may be head trauma, lumbar puncture, presumed viral infection, or idiopathic.

Convergence paralysis is also an acquired concomitant supranuclear gaze disorder the deviation of which is equal in all positions of gaze. Full adduction is present during conjugate eye movements. This condition is difficult to differentiate from convergence insufficiency, and can be caused by ischemia, demyelinating disease, or influenza infection.

Skew Deviation

Skew deviation is a concomitant or noncomitant (paralytic) vertical deviation and is invariably present with other neurologic signs. Skew deviation is associated with posterior fossa disease. INO often presents with unilateral hypertropia, causing a skew deviation.

The Differential Diagnosis of Gaze Abnormalities

Gaze palsies result in an inability to produce saccadic or pursuit eye movements, and are caused by lesions anywhere from the cerebral cortex to the PPRF.

Gaze palsies can be classified as horizontal and vertical gaze palsies. Horizontal gaze deficits may occur because of developmental anomalies in the motor neurons of the abducens nuclei, in intrinsic brainstem disease, as in INO, or in PPRF lesions, causing pontine gaze paralysis.

Vertical gaze palsies occur in pretectal disease (loss of downgaze), aqueductal stenosis, tumors of the pineal

gland, and MS, causing Parinaud's syndrome (loss of upgaze). Progressive supranuclear palsy, Parkinson's disease, and chronic progressive supranuclear palsy (PSP) may demonstrate combination losses of upgaze and downgaze.

Horizontal Gaze Palsies

Congenital absence of all horizontal conjugate eye movements occurs in familial paralysis of horizontal gaze. This paralysis is a rare condition and is theorized to result from a developmental anomaly of the abducens motor nuclei.

An example of a more common horizontal gaze palsy is INO, caused by a lesion in the MLF between the abducens and oculomotor nuclei. The hallmark sign of INO is a lag of the ipsilateral medial rectus muscle when adducting. The contralateral eye exhibits an abducting nystagmus, although the origin of this nystagmus is unknown (Figure 17-20).

Multiple sclerosis is the most likely cause of an INO in a young adult. If the INO patient is older than 50 years, then brainstem vascular occlusive disease should be considered.

If the INO is produced by a midbrain lesion, it is usually bilateral (a "BINO"), is characterized by an absence of convergence, and is called an anterior INO. A bilateral abduction nystagmus will be present. If the patient is exotropic (a "WEBINO"), the medial rectus nuclei or MLF may be involved. A posterior INO is the result of a lesion in the sixth-nerve nuclei in the pons and produces an abduction deficit.

A horizontal gaze paresis may occur in lesions of the PPRF, which produces an ipsilateral conjugate horizontal gaze palsy. If the ipsilateral PPRF (or abducens nuclei) and the parabducens nuclei are involved, this will produce a total horizontal gaze paralysis of both eyes toward the side of the lesion. If a lesion of the ipsilateral MLF also occurs, then the ipsilateral eye also fails to make a contralateral gaze motion. This is called a one-and-a-half syndrome. These patients will usually appear exotropic. In this syndrome, the eye ipsilateral to the lesion will be totally immobile during attempted horizontal gaze motions, and the contralateral eye will only be able to abduct (Figure 17-21).

Vertical Gaze Palsies

Isolated upgaze and downgaze palsies remain rare disorders. Pretectal disease causes isolated downgaze palsies, and lesions of the posterior commissure produce isolated upgaze palsies.

Parinaud's syndrome usually presents as a paresis of saccadic upgaze. The patient usually first notices

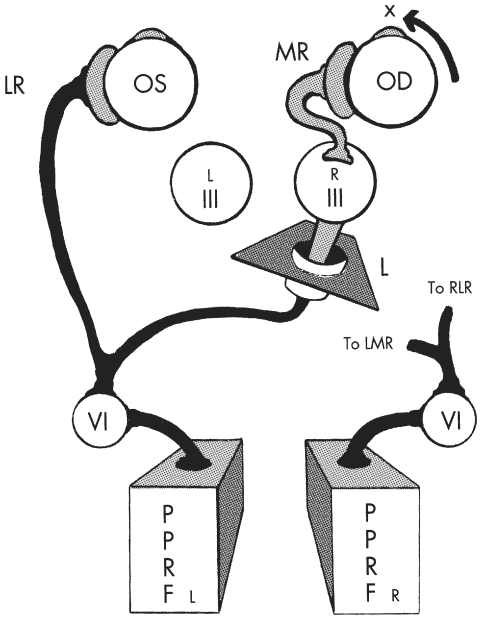


FIGURE 17-20 ■ Internuclear ophthalmoplegia. *RPPRF,* Right paramedian pontine reticular formation; *LPPRF,* left paramedian pontine reticular formation; *VI,* sixth nerve nucleus; *RLR,* right lateral rectus muscle; *LMR,* left medial rectus muscle; *L,* lesion of right medial rectus muscle; *R III,* right third nerve nucleus; *L III,* left third nerve nucleus; *MR,* right medial rectus muscle; *LR,* left lateral rectus muscle; *OD,* right eye; *OS,* left eye; *X,* adduction deficit of OD. (From Blaustein BH, ed: *Ocular manifestations of neurologic disease,* St Louis, 1996, Mosby. Illustration by B. Muchnick.)

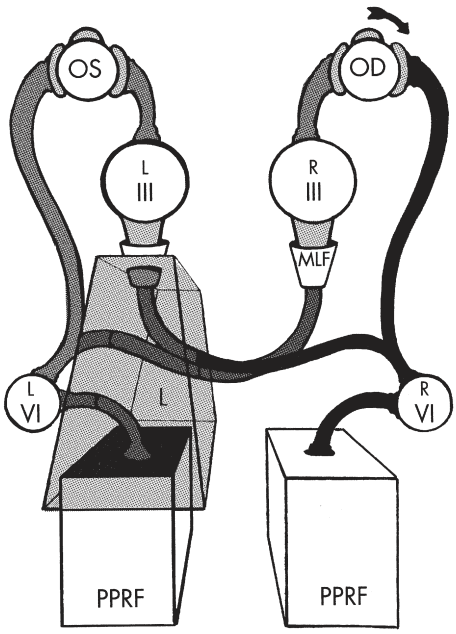


FIGURE 17-21 ■ One half syndrome. *PPRF,* Paramedian pontine reticular formation; *R VI,* right sixth-nerve nuclei; *L VI,* left sixth-nerve nuclei; *L,* lesion of the left MLF and PPRF; *MLR,* medial longitudinal fasciculus; *R III,* right third-nerve nucleus; *L III,* left third-nerve nucleus; *OD,* right eye; *OS,* left eye. (From Blaustein BH, ed: *Ocular manifestations of neurologic disease,* St Louis, 1996, Mosby. Illustration by B. Muchnick.)

this when playing sports. He or she may lose the ability to gaze upward to shoot a basketball or serve a tennis ball. Clinically, on attempted superior gaze, the eyes will converge and retract into their orbits. This reflex is the result of stimulation of both medial recti muscles by the third-nerve nucleus. Other findings in Parinaud's syndrome include partial third-, fourth-, or sixth-nerve palsies, skew deviations, papilledema, middilated light-near dissociation pupils, and lid retraction (Collier's sign). Causes of Parinaud's syndrome include trauma, stroke, MS, neurosyphilis, aqueductal stenosis, and pineal gland tumors.

Combination Upgaze and Downgaze Palsies

Three disorders that can have a combined upgaze and downgaze paresis are progressive supranuclear palsy (PSP), Parkinson's disease, and chronic progressive external ophthalmoplegia (CPEO). These disorders are caused by supranuclear lesions, although ocular motor nuclei may be involved. Progressive supranuclear palsy and Parkinson's disease have been discussed previously in this chapter.

CPEO actually refers to a number of clinical symptoms marked by the development of slowly progressing external ophthalmoplegia. This disorder appears clinically similar to progressive supranuclear palsy. Chronic progressive external ophthalmoplegia has been classified by Rowland into ocular myopathies (i.e., Graves' disease; orbital pseudotumor), neuromuscular junction disorders (i.e., myasthenia gravis), neural myopathies, and uncertain origins. Debate exists as to whether CPEO is neurologic or myopathic in nature.

Summary

* Supranuclear motility disorders rarely produce the complaint of diplopia.

* A thorough clinical examination of the patient, combined with an understanding of the relevant neuroanatomy, should approximate the area involved and perhaps generate a differential diagnosis. Further neuroinvestigative techniques, such as radiologic examination, should pinpoint the involved area and, when combined with laboratory and other physical examination findings, pinpoint the cause of the disorder.

Clinical Examination of the Supranuclear System

History

Patients with disorders of the supranuclear system rarely have complaints of diplopia on the initial visit. The examiner should note whether the patient is experiencing any significant neurologic problems such as headache, paresthesias, anesthesias, amnesias, and loss of vision. The following text outlines the functions that should be evaluated in the examination, and the tests that should be used.

Preliminary examination
(a) Visual acuity
(b) Visual fields
(c) Color vision
(d) Stereopsis testing
(e) Contrast sensitivity

Range of motion
(a) Ductions
(b) Versions

Alignment of visual axis
(a) Red glass test
(b) Maddox rod test
(c) Cover-uncover
(d) Alternate cover

Saccades and nystagmus
(a) Rule out nystagmus and inappropriate saccades in primary gaze
(b) Note latency, velocity, and accuracy of saccades

Vestibular testing
(a) Visual acuity during head shaking
(b) Ophthalmoscopy of retinal structures to detect micronystagmus
(c) Caloric testing

Smooth pursuit tests
(a) Patient to track small object

Vergence testing
(a) Test fusional amplitudes
(b) Near point of convergence

The Infranuclear Motility System

Most cases of paralytic strabismus, if not restrictive in nature or secondary to myasthenia gravis, are caused by lesions affecting the ocular motor cranial nerves, their fascicles, or their nuclei. The recognition that a problem exists will begin either with symptomatic complaints by the patient of diplopia, or with objective clinical signs of ocular motor paresis on ductions, versions, red glass, Maddox rod, cover-uncover, and alternate-cover testing. Also, if the patient exhibits a head tilt or turn, no matter how subtle, this may be another indication of a potential ocular misalignment.

Once the examiner has determined that a potential ocular motor palsy exists, it is essential to isolate the nerve or nerves involved, on the basis of the affected motility pattern. Having pinpointed the nerve or nerve group involved, the location of the lesion, whether in the nucleus, fascicle, nerve, neuromuscular junction or muscle, can be predicted on the basis of the history, age of the patient, motility pattern, and concurrent neurologic signs. Finally, on the basis of the above factors, a differential diagnosis is developed. Accurate diagnosis and pinpointing of the lesion's location requires consultation with such medical specialties as radiology, neurology, and endocrinology.

Three cranial nerves control ocular motor motility. These are the oculomotor nerve (cranial nerve III), the

trochlear nerve (cranial nerve IV), and the abducens nerve (cranial nerve VI).

Higher cortical centers in the brain control the nuclei of each nerve to allow precise alignment and movement of the eye. Lesions of these supranuclear centers, as previously discussed, cause gaze palsies as the result of a combinational loss of muscle groups. This rarely produces the complaint of diplopia.

Lesions of the infranuclear areas, including the nerve nuclei, fascicles, nerve, neuromuscular junction, or muscle, may produce single or combinational ocular motor palsies. If a lesion occurs in isolation, and only one nerve is affected, then a distinctive pattern of motility deficit is usually readily recognizable. More complicated nerve combinational losses may produce a variety of abnormal motility patterns that require an extensive diagnostic work-up. By determining which ocular motor nerves are affected and understanding the significant neuroanatomy, the location of the lesion may be approximated and then a differential diagnosis may be generated based on location of the lesion and the significant epidemiology of the case. Actual diagnosis usually requires radiologic imaging and neurologic consultations.

Oculomotor Nerve Palsy

Functional Anatomy of the Third Cranial Nerve

The third cranial nerve supplies somatic motor fibers to the medial rectus for adduction, inferior rectus for downgaze, inferior oblique and contralateral superior rectus for upgaze, and both of the levator palpebrae superioris muscles for elevation of both lids. This nerve also provides parasympathetic input to the constrictor pupillae of the papillary miosis, and the ciliary muscles of the ciliary body for accommodation.

The nuclei of the somatic motor component lie near the midline of the midbrain at the level of the superior colliculus. The MLF is located just lateral and inferior to the third-nerve nuclei. The oculomotor nuclear complex contains subnuclei that supply individual muscles.

After the lower motor neurons leave the oculomotor complex, they course through the red nucleus and emerge in the interpeduncular fossa between the pons and the midbrain. Near this region, these motor fibers combine with parasympathetic fibers from the Edinger-Westphal nucleus. Together they form the oculomotor nerve, which passes anteriorly through the dura and enters the cavernous sinus. The third nerve courses through the cavernous sinus superior to the trochlear nerve, passes through the superior orbital fissure, where it branches into a superior and inferior division, and then enters the orbit. The inferior division innervates the medial rectus, inferior oblique, and inferior rectus muscles. The superior division innervates the levator palpebrae superioris and superior rectus muscles. The parasympathetic fibers branch off the inferior division to terminate in the ciliary ganglion.

The Diagnosis of Oculomotor Nerve Palsy

The diagnosis of third-nerve palsy is best approached anatomically, because a characteristic pattern of functional loss is dependent on the location of the lesion along the path of the nerve.

Nuclear Third-Nerve Lesions

We can predict what would happen in a hypothetical patient with a complete nuclear third-nerve lesion. A unilateral third-nerve palsy would be present, with the eye appearing "down and out" and unable to accommodate. Paralysis of the contralateral superior rectus muscle, as well as a bilateral ptosis (because the levator is bilaterally innervated) would be present. Also, the ipsilateral pupil would be dilated and unreactive to direct or consensual stimuli.

Isolated complete lesions of the oculomotor nuclei are virtually unheard of, because infarcts affecting these nuclei would also involve surrounding areas, causing vertical gaze palsies. There are reported cases of single third-nerve muscle paresis involving just a few muscles and the pupil, but concurrent neurologic signs were always present. Specific mesencephalon lesions were postulated (by Waring and others) to explain these cases. Also, cases of congenital third-nerve palsies may exist, but these tend to be incomplete and unilateral.

Fascicular Third-Nerve Lesions

As the fascicles of the oculomotor nerve leave the nuclear area and pass through the midbrain, they may be subjected to lesions the location of which may be inferred from concurrent neurologic deficits. The adjacent structures most commonly affected include the red nucleus, cerebral peduncle, and the entire brainstem.

If a patient with a third-nerve palsy has a contralateral cerebellar ataxia and slow tremor, this implies involvement of the third nerve and the adjacent red nucleus. This condition is called Claude's syndrome.

A lesion affecting the cerebral peduncle along with the adjacent third nerve produces a third-nerve palsy with contralateral hemiparesis and is called Weber's syndrome.

If a large lesion, usually produced by an infarct or tumor, involves the third nerve, red nucleus, and cerebral peduncle, then Benedikt's syndrome is produced. If this is accompanied by a vertical-gaze palsy, then Nothnagel's syndrome results.

Precavernous Third-Nerve Palsies

Lesions affecting the oculomotor nerve as it passes from the brainstem to the cavernous sinus arise from aneurysm, infection, blood problems, and tumor.

Differentiation of these causes in the office is helped by the presence or absence of the concurrent symptoms and clinical signs of pain and papillary involvement. Third-nerve palsy associated with orbital and facial pain may be caused by compression of the oculomotor neural bundles as they pass by an aneurysm of the posterior communicating artery. Furthermore, the aneurysm typically produces a dilated pupil and ptosis in conjunction with the third-nerve palsy.

During cerebral herniation, the uncus of the temporal lobe may compress the third nerve against the clivus or the temporal edge, producing mydriasis, followed by external ophthalmoplegia.

Cavernous Sinus Third-Nerve Palsies

As the third nerve passes through the cavernous sinus, it is susceptible to aneurysm, thrombosis, tumor, infection, and inflammation. Usually the fourth and sixth nerve also are involved, producing a combinational nerve palsy.

A patient seen with a third-nerve palsy who has ptosis, diplopia, and facial pain with trochlear and abducens nerve involvement may have a compressional effect from an aneurysm.

Intraorbital Third-Nerve Palsies

Isolated lesions of either the superior or inferior branches of the third nerve have been known to occur. An isolated lesion to an individual muscle is rare. All cases of isolated inferior branch palsies (presumed to be viral) have recovered spontaneously (Susac). Isolated inferior rectus muscle palsies have also recovered spontaneously.

Other Cases of Third-Nerve Palsies

Infarction of the oculomotor nerve may result from diabetes, collagen-vascular disease, and hypertension. Along with aneurysm, vascular disease caused by diabetes mellitus and hypertension are the most common causes of third-nerve palsies. The lesion in diabetes has been found on pathologic sectioning to be present in the cavernous sinus or subarachnoid areas.

The presenting feature in diabetic third-nerve palsy may be facial pain, followed by diplopia or ptosis. The pain then abates. The pupil is usually spared in diabetic third-nerve palsy, unlike aneurysmal third-nerve involvement. Third-nerve palsy can be the presenting symptom of diabetes.

Severe head trauma that leads to bone fracture and unconsciousness can cause an oculomotor palsy. Traumatic injury to the nerve can occur as it exits the brainstem, in its subarachnoid portion, or as it enters the supraorbital fissure. Twelve percent of patients with giant cell arteritis are seen with third-nerve palsy, requiring an erythrocyte sedimentation rate and possible temporal artery biopsy for positive confirmation of the disorder.

Aberrant Regeneration

After oculomotor palsy resulting from trauma, migraine, and aneurysm, the third-nerve fibers may resprout and innervate different muscles. This process causes anomalous synkinesis effects such as lid elevation and miosis during adduction or downgaze, lid depression or abduction, and absence of pupil response. Aberrant regeneration in the absence of a third-nerve palsy may indicate a mass lesion of the cavernous sinus.

Pupil Involvement in Third-Nerve Palsies

If a patient with third-nerve palsy is seen with orbital pain, it may be the result of either an aneurysm or vascular-occlusive disease such as diabetes. If it is the result of aneurysm, arteriography is essential for diagnosis. This technique has an inherent risk of significant morbidity, however, and is thus not to be performed unless an aneurysm is highly suspected and vascular-occlusive disease has been ruled out.

In 1960 Goldstein and Cogan showed that papillary sparing occurs in 80% of patients with vascular-occlusive third-nerve palsy, but in less than 10% in patients with aneurysmal third-nerve palsy. Therefore, a third-nerve palsy with pupil involvement may be the result of aneurysm and may require an arteriography. A third-nerve palsy with pupil sparing is usually the result of vascular-occlusive disease, although it may be found to be spared in early aneurysmal cases, and arteriography should only be considered if additional signs point to a vascular abnormality.

The explanation for pupil-sparing third-nerve palsies may be found in the anatomical location of the papillary fibers. They lie superficially on the nerve, so they are susceptible to compressional lesions like aneurysms. Vascular-occlusive diseases infarct the central nerve while sparing most of the superficial pupil fibers, however, and so the pupil is relatively spared.

Third-Nerve Palsies in Children

Almost half of the cases of oculomotor palsies in children are congenital, and a fourth are traumatic. Neoplasms and aneurysms account for most of the remaining cases. Most cases of congenital third-nerve palsy exhibit aberrant regeneration. Birth trauma is assumed to be the likely cause.

Management of Third-Nerve Palsies

Patients younger than 40 who are seen with isolated third-nerve palsies require a CT scan, cerebrospinal fluid study, and cerebral angiography, whether or not the pupil is spared. Patients older than 40 with pupil-sparing oculomotor palsies are assumed to have vascular-occlusive disease, and are therefore just observed weekly

for 1 month, and then every month for 6 months. These patients should have a blood pressure and diabetes work-up. Any sign of pupil involvement in these older patients requires an immediate arteriography, CT scan, and cerebrospinal fluid examination.

Trochlear Nerve Palsy

Functional Anatomy of the Fourth Cranial Nerve

The fourth, and smallest, of all cranial nerves supplies somatic motor fibers to the superior oblique muscle of the eye. The nucleus of the trochlear nerve is located in the midbrain at the level of the inferior colliculus, near the midline, at the caudal end of the third nerve complex.

As the axons leave the nucleus dorsally, they decussate (the only cranial nerve that does so) to eventually innervate the contralateral superior oblique muscle.

After decussation, the axons proceed ventrally as they curve forward and around the cerebral peduncle, piercing the dura anteriorly with the third nerve.

The fourth nerve then enters the cavernous sinus, running along its lateral wall, through the superior orbital fissure to enter the eye. This represents the longest intracranial course of any cranial nerve. The tendon of the muscle then courses through the trochlea and is contiguous with the superior oblique. Stimulation of the fourth nerve causes contraction of the superior oblique muscle, thus depressing, abducting, and intorting the eye.

The Diagnosis of Trochlear-Nerve Palsy

Any patient seen with a vertical muscle weakness must be worked up for trochlear-nerve palsy. If a palsy exists, the affected eye will exhibit a hyperdeviation and a weakness to lateral and downward gaze. This condition is best diagnosed by a four-step procedure that includes the Bielschowsky head tilt test.

To isolate which muscle is causing the vertical deviation, the examiner should proceed with the following four steps.

1. Determine which eye is hypertropic or hyperphoric. The patient should stare straight ahead in primary gaze. The hypertropia may be obvious, or Maddox Rod with or without cover-uncover or alternate-cover testing may be necessary. A vertical prism bar is used to measure the vertical component.
2. Determine if the vertical deviation is greatest to left or right gaze. The patient should follow the target to his or her left and then to his or her right. The examiner may be able to see which direction or gaze causes a worsening hypertropia. If not, red lens or Maddox Rod testing with a vertical prism bar can measure the hyperdeviation to left or right gaze.
3. Determine if the deviation is greatest on upgaze or downgaze when the patient is looking to the affected side. Once the examiner has determined the horizontal gaze that causes the greatest deviation, the patient should look in that direction, and then attempt to elevate and depress the eyes. The examiner may see an obvious worsening of the vertical deviation to either superior or inferior gaze, or the red lens or Maddox Rod/Prism Bar test may need to be used.
4. Determine if the hyperdeviation is greatest in left head tilt or right head tilt. While the patient is staring straight ahead in primary gaze, the examiner should have them tilt his or her head to the left and then the right. The examiner may see which head tilt worsens the vertical deviation (this will be opposite the head tilt the patient prefers), or the Maddox Rod/Vertical Prism Bar test may need to be used.

To better understand the testing procedures for the diagnosis of vertical ocular motor deviation, we will present a case example (Figure 17-22, *A* to *D*).

A patient is seen with complaints of sudden onset of diplopia. In questioning the patient, the examiner finds that the diplopia is vertical in nature. The following three-step procedure is a typical testing procedure for this vertical deviation.

1. In primary gaze. With a Maddox Rod oriented vertically (to produce a horizontal red line image) in front of the right eye, the examiner should hold a white light 24 inches from the patient. The patient, staring straight ahead at the two images, notes that the red line is below the white light. Therefore, the right eye is the hyperdeviated eye. This condition may result from a weakness in the depressors of the right eye (the right inferior rectus [RIR] or right superior oblique [RSO]), or a weakness in the elevators of the left eye (the left superior rectus [LSR] or left inferior oblique [LIO]). The possible muscle affected has been narrowed from eight to four (see Figure 17-22, *A*).
2. In horizontal gaze. Now the examiner asks the patient to look left and right through the Maddox Rod and prism bar. The patient notes that on right gaze the white light is almost touching the red line. Therefore, no hyperdeviation exists in this position of gaze. But on left gaze, the red line is well below the white light, even further than when looking straight ahead! Because the weakness is worse to left gaze, it may be the result of a weakness in the muscle that helps the right eye depress when adducting (RSO), or may be due to weakness of the muscle that helps the left eye elevate when abducting (LSR). The field of possible muscles has been narrowed to two (see Figure 17-22, *B*).
3. In vertical gaze. Finally, while this patient is looking toward the horizontal direction that causes the greatest vertical deviation (in this case, the left), the

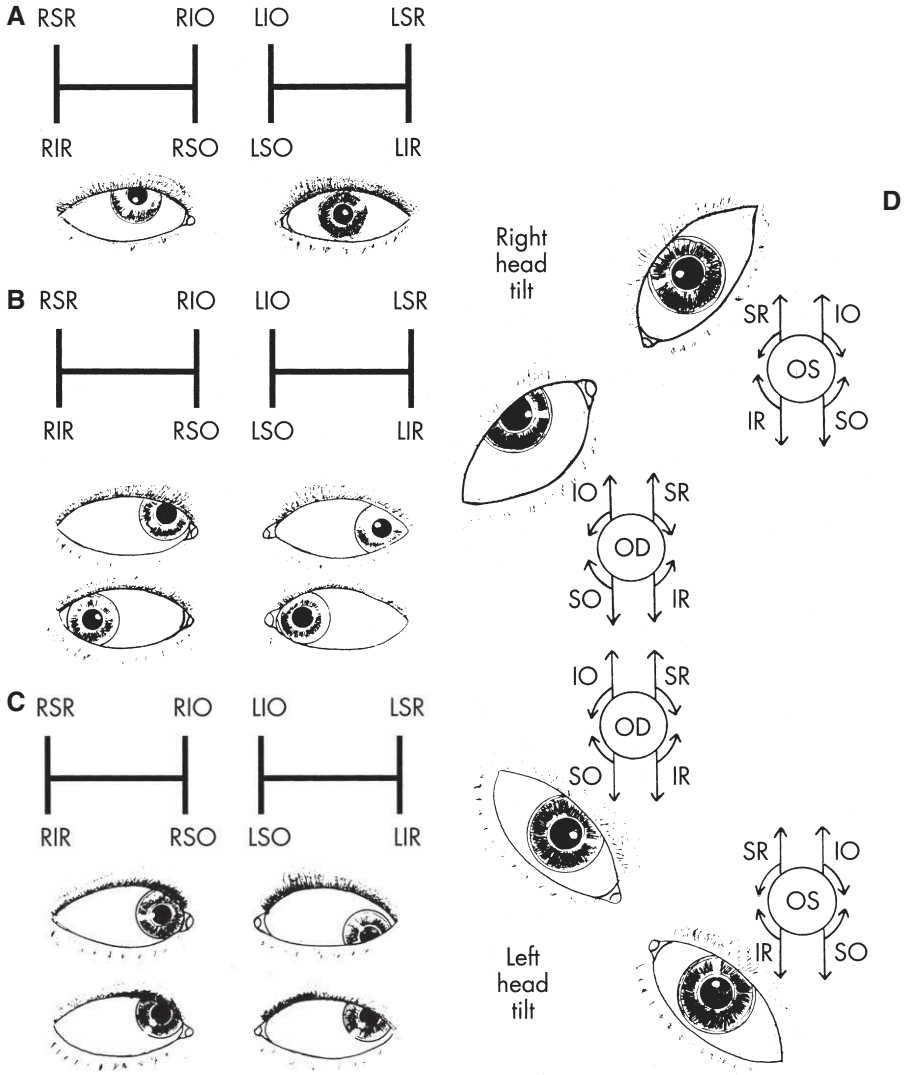


FIGURE 17-22 ■ **A,** Primary gaze. **B,** Horizontal gaze. **C,** Vertical gaze. **D,** Bielschowsky head tilt test. (From Blaustein BH, ed: *Ocular manifestations of neurologic disease,* St Louis, 1996, Mosby. Illustration by B. Muchnick.)

target light is lifted upward, above horizontal. In this position, the patient notes little separation of the white light from the red line. Therefore, the elevator of the left eye in this position (LSR) is not affected. But as the light is brought down below the horizontal meridian, the patient notes increasing separation. This perception implicates the depressor muscle of the right eye in this position (RSO) as the muscle involved (see Figure 17-22, *C*).

These three steps will diagnose most acute muscle palsies, but with time there is a "spread-of-concomitance" so that the deviations become equal in all directions of gaze. This spread-of-concomitance makes the three-step diagnosis equivocal, because the patient may, with time, fixate with the affected eye. The Bielschowsky head tilt test can help to diagnose this particular problem. Consider the above case with this method.

Head tilt testing. The patient looks through the Maddox Rod in front of the right eye and the vertical prism bar in front of the left eye. This patient then tilts his or her head first to the left. When performing this maneuver, the right eye must extort by stimulation of the RIR and the RIO, and the left eye must intort by stimulation of the LSR and the LSO. The patient notices no increase in the separation of light from the bar, so no increase in hyperdeviation exists when tilting to the left.

However, when the patient tilts his or her head to the right, he or she sees the white light move well above the red line. This implies an increasing right hyperdeviation. To decide what muscle is involved, look at what happens as the head is tilted to the right. The right eye must now intort, using stimulation of the RSO and the RSR. The left eye must extort using the LIR and the LIO. But, because it is a right hyper-

deviation, it must be either the right depressor and intorter (RSO) or the left elevator and extorter (LIO). It cannot be the LIO, however, because when the patient looked to the right in horizontal gaze testing (step 2), no vertical deviation was present. If an LIO palsy was present, step 2 would have shown a vertical deviation to the right as opposed to the left gaze (as in this case). Therefore, the Bielschowsky head tilt test has shown the affected muscle to be the RSO, independent of the presence of a spread of concomitance (Figure 17-22, *D*).

The diagnostic approach should be anatomical and should rule out nuclear, fascicular, subarachnoid, cavernous sinus, superior orbital fissure, and orbital causes.

Nuclear and Fascicular Fourth-Nerve Palsy

Nuclear and fascicular fourth-nerve palsies are rare. The fourth nucleus also may be absent or congenitally hypoplastic. The nucleus also may be affected by neurosurgical intervention, trauma, brainstem tumors, hemorrhage, infarction, or demyelinating disease.

Subarachnoid Fourth-Nerve Palsy

Head trauma is the most common cause of trochlear nerve palsy, because frontal head injury can cause a contrecoup shock wave to disrupt one or both fourth nerves as they emerge together in the anterior medullary velum (anterior roof of the fourth ventricle). This process produces a unilateral or bilateral fourth-nerve palsy.

Bilateral trochlear-nerve palsy produces an alternating hyperdeviation that depends on the direction of horizontal gaze. Other causes of subarachnoid trochlear involvement include posterior communicating or basilar artery aneurysm, infarction due to diabetes, tumor, or meningitis.

Cavernous Sinus and Superior Orbital Fissure Fourth-Nerve Palsy

After trauma, infarction caused by diabetes is the most common cause of fourth-nerve palsies, and accounts for one fifth of all cases. This prognosis for recovery is better than in traumatic injury. If the palsy occurs in the fourth to fifth decades, almost all cases improve spontaneously within 6 months. Other causes of cavernous sinus fourth-nerve palsy include aneurysm, tumor, herpes zoster, and carotid-cavernous fistula.

Orbital Fourth-Nerve Palsy

If a patient with normal eye posture in the primary position of gaze, but on adduction the eye depresses and cannot elevate well, then Brown's superior oblique tendon syndrome must be suspected. The affected eye elevates well in the abducted position.

This syndrome may be congenital or acquired. It is caused by a shortened superior oblique muscle tendon, so when adducting the sheath is taut, thus limiting elevation of the eye. When abducting, the sheath is looser, allowing elevation. Surgical intervention is necessary for correction of this syndrome.

Fourth Cranial-Nerve Palsy in Children

Most cases of childhood fourth-nerve palsy are congenital, although one third may be from trauma. If a sudden onset of vertical diplopia is found in a patient in their first to third decade of life, with no history of trauma or with no concurrent neurologic signs, then most likely this patient has a decompensating phoria. The presence of large fusional amplitudes will help in this diagnosis. Symptoms of diplopia or headache may be relieved by prescribing vertical prisms.

Management of Fourth-Nerve Palsies

Most cases of fourth-nerve palsies are traumatic in origin or decompensating phorias. Any patient, of any age, with a traumatic sudden onset of trochlear palsy who has large vertical fusional amplitudes needs no extensive neurologic work-up, because it is congenital in nature. If there are no significant fusional amplitudes, then a Tensilon test is mandatory to rule out myasthenia gravis, and radiologic tests must be used to rule out a compressive tectal lesion. If the Tensilon test is negative, the patient should have a general systemic work-up to rule out diabetes or hypertension as a possible cause of infarct.

Because isolated nonischemic fourth-nerve palsies are rare, in-depth neurologic investigations should only proceed if a progression of clinical signs and symptoms is present. These cases require a CT scan and cerebral angiography.

Abducens Nerve Palsy

Functional Anatomy of the Sixth Cranial Nerve

The abducens nerve is a somatic motor nerve that innervates the lateral rectus of the eye. When contracted, the lateral rectus muscle acts to abduct the eye.

The nucleus of the abducens nerve is close to the midline, ventral to the fourth nerve, in the pontine tegmentum. Axons from the nucleus project ventrally, emerging at the ventral surface of the brainstem between pons and medulla. Running ventrally, the abducens nerve pierces the dura, bends around the petrous portion of the temporal bone, and enters the cavernous sinus. It runs lateral to the internal carotid artery and medial to the other nerves of the cavernous sinus, and enters the eye in the medial superior orbital fissure. Once entering the orbit, it innervates the lateral recti muscle.

The Diagnosis of Abducens Nerve Palsy

Even though sixth-nerve involvement is the most commonly reported of the ocular muscle palsies, no definitive diagnosis is made in approximately one quarter of the cases. The most common cause of abducens nerve palsies is most likely ischemia to the nerve secondary to diabetes or hypertension. As in third and fourth-nerve palsies, restoration of nerve function occurs in 3 to 6 months.

As with the other ocular motor nerves, diagnosis should be consistent with the location of the lesion along the path of the sixth nerve, from nucleus to orbit.

Nuclear and Fascicular Abducens Nerve Palsies

Nuclear sixth-nerve palsies are usually the result of developmental abnormalities, injury, or tumor, and are typically characterized by horizontal gaze palsy.

As the fascicles of the sixth nerve pass the pyramidal tract (through medial pons), they are susceptible to infarction of the medial inferior pons, producing ipsilateral abducens palsy and facial weakness with contralateral hemiplegia. This condition is known as Millard-Gubler syndrome. Demyelinating disease also may affect the fascicular sixth-nerve area.

Subarachnoid Sixth-Nerve Palsy

In its subarachnoid region, the sixth nerve may be compressed by berry aneurysm or tumor, disrupted by trauma or meningitis, or lesioned during neurosurgical intervention.

Petrous Sixth-Nerve Palsy

As the sixth nerve courses over the petrous portion of the temporal bone, it may be disrupted by temporal bone fractures secondary to trauma.

This nerve is also susceptible to infection from the mastoid process, which, if also affecting the nearby fifth (trigeminal) cranial nerve, causes an abducens palsy, facial pain, and possible deafness. This condition is known as Gradenigo's syndrome. If not caused by tumor, the prognosis in most cases of Gradenigo's syndrome is for full and spontaneous recovery.

Cavernous Sinus and Orbital Abducens Nerve Palsy

As with other ocular motor nerves, the sixth cranial nerve is susceptible to internal carotid artery aneurysm, carotid-cavernous fistula, tumor, and herpes zoster while in the cavernous sinus. Tumors, such as nasopharyngeal carcinoma, may affect the sixth nerve as it passes into the orbit.

Sixth-Nerve Palsies in Children

Tumor should be suspected in all cases of abduction weakness in children. It is essential to look for any cerebellar signs, papilledema, or worsening of the palsy over time, which would indicate an expanding space-occupying lesion. Trauma is another common cause of abducens nerve palsy in childhood (40% of cases in one study). All cases of ocular motor palsy in children should be evaluated for battered child syndrome.

Virus also may cause sixth-nerve palsies in children. Neurologic examination (with CT scan, cerebrospinal fluid study, and Tensilon test) will be negative and most cases recover spontaneously.

Duane's Retraction Syndrome

Three forms of Duane's retraction syndrome exist, although all are associated with narrowing of the palpebral fissure (apparent globe retraction) on adduction. This syndrome is more common in women and girls, and may be unilateral or bilateral, although the left eye is affected more than the right.

Type 1 Duane's has limited abduction but normal adduction; type 2 is characterized by normal abduction but poor adduction; and type 3 exhibits limited abduction and adduction. There is no treatment necessary in cases of Duane's syndrome because these patients rarely complain of diplopia and maintain good stereopsis in primary gaze.

Bilateral Sixth-Nerve Palsies

Most cases of bilateral abducens palsy are caused by neoplasm. The second most common cause was demyelinating disease. It is important to know that bilateral sixth nerve palsies are never caused by infarction, so an atraumatic patient seen with this disorder requires a work-up to rule out space-occupying lesions, multiple sclerosis, subarachnoid hemorrhage, and infection.

Management of Sixth-Nerve Palsies

A sixth-nerve palsy in a child with no history of trauma should be observed every few weeks. If progression of the paresis is observed, then a neurologic work-up to rule out neoplasm is warranted. Usually young patients who do not improve in 6 months receive cranial imaging, but in most cases, no lesions are found. Surgery may eventually help these patients.

Those patients in the second to fourth decade of life who are seen with acute isolated sixth nerve paresis should have a medical examination to rule out diabetes mellitus, hypertension, and collagen-vascular disease, and a neurologic evaluation to rule out myasthenia gravis. Usually patients are just observed until improvement is noted (usually in 6 months).

After the age of 40, patients with sixth-nerve palsy caused by infarction usually are seen with orbital pain. These patients should be examined for diabetes mellitus and hypertension, and erythrocyte sedimentation rate tested to rule out giant cell arteritis.

Any patient with sixth-nerve palsy with ipsilateral facial pain must have a CT scan of the mastoid to rule out Gradenigo's syndrome secondary to inflammation, infection, or a tumor of the tip of the petrous pyramid.

All bilateral sixth-nerve patients must have a neuroradiologic examination to rule out a tumor causing increased intracranial pressure. Also, papilledema should be ruled out in these cases.

Combination Ocular Motor Palsies

Multiple ocular palsies can arise from lesions anywhere from their nuclear areas to the orbit. Many occur where the nerves lie close together in the cavernous sinus, and a number of conditions can cause combinational losses. These conditions include aneurysm, tumor, diabetic-induced infarction, and herpes zoster. If other signs are present, such as orbital pain caused by trigeminal involvement, this further supports a cavernous sinus location. If visual loss is a concurrent sign, then the lesion is more likely near the orbit where the second (optic) cranial nerve is closest to the ocular motor bundles.

Trauma is a significant cause of multiple ocular motor nerve palsies. Injury can occur in the subarachnoid and orbital regions. The trauma usually must be severe to cause multiple loss.

Exposure to toxic environmental poisons also can cause ocular motor combined palsies. The location of the lesion remains uncertain.

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CHAPTER 18

Headache

CHAPTER OUTLINE

Headache can be one of the most disabling painful episodes that a patient may ever experience. Although most headaches are benign, some represent the first clinical symptom of a serious and potentially life-threatening underlying systemic disease. The optometrist will often be the first health professional a headache patient contacts to determine the cause of their head pain. Therefore, the primary care optometrist is in a unique position to evaluate the headache patient, exclude ocular causes of the head pain, and suggest an appropriate subspecialty referral.

Within the head and neck there are structures that are extremely sensitive to pain. These pain sensitive structures include the muscles, nerves, meninges, and blood vessels both within the cranial vault and around the skull. A process that distends, compresses, displaces, or inflames any of these structures is likely to produce pain.

Within the cranial vault are the venous sinuses, arteries, the cranial nerves, and the brainstem gray matter, all of which are sensitive to pain. Around the skull is the periosteum, the skin, muscles and arteries, cranial nerves, special sense organs, and the mucous membranes, all of which are exquisitely sensitive to manipulation of any kind.

Headache can emanate from a variety of sources (Tables 18-1 and 18-2). Some etiologies are life-threatening, and others are disabling but without serious systemic implications. A headache history should include questions, such as associated signs and location, that probe the possibility of an underlying disorder.

Headache with associated symptomology is often an indicator of an underlying systemic disease. Cancer and giant cell arteritis may be seen as headache with weight loss. A headache with fever and chills may be the result of a systemic infection. Migraine headache is often associated with vomiting and diarrhea.

The location of the headache is often invaluable when attempting to develop a differential diagnosis. For example, tension headaches are typically bilateral, and migraine and cluster headaches are usually unilateral in their presentation.

The time of onset is an important distinguishing feature of headache. Head pain that is worse in the morning mandates an exclusion of an intracranial tumor and sinusitis. If a patient is awakened during sleep by head pain, then the likely diagnosis is cluster headache. Tension-type headache is classically worse at the end of the day.

Many patients suffer head pain, and headache is the chief complaint of almost 5% of all medical office visits.

Headache is characterized as chronic, subacute, and acute. This differentiation is crucial when excluding an ocular-associated headache and when considering referral for a medical evaluation.

PRIMARY CHRONIC HEADACHE

Chronic headaches are typically benign and occur during several years. Often chronic headaches vary little in their presentation. Although recurrent, each episode is of roughly the same intensity. Consistency in intensity, frequency, duration, and presentation is characteristic of chronic, primary headache, and typically indicates a benign etiology. Types of chronic headache

TABLE 18-1 CHARACTERISTICS OF HEADACHE SYNDROMES

	CLASSIC MIGRAINE	COMMON MIGRAINE	CLUSTER HEADACHE	TENSION HEADACHE	SINUS HEADACHE	TEMPORAL ARTERITIS	INTRACRANIAL PRESSURE	SUBARACHNOID HEMORRHAGE	MENINGITIS
Age at onset	Adolescence	Adolescence or young adulthood	Age 20-50	Any age	Any age	Over 60	Any age	Any age	Any age
Gender	F > M	F > M	M > F	Both	Both	Both	Both	Both	Both
Quality of pain	Throbbing, pulsatile	Dull, aching	Sharp, stabbing	Pressure	Pressure	Burning	Dull ache	Sharp, stabbing	Dull soreness
Location of pain	Unilateral, frontal	Unilateral or bilateral	Behind one eye	Sides and back of head	Frontal, maxillary regions	Temporal scalp	Entire head	Entire head	Entire head
Diurnal pattern	Variable	Variable	Daily, nocturnal, seasonal	Late in day	None	Worse at night	Worse in morning	None	None
Aggravating factors	Bright light, noise	Bright light, noise	Alcohol	Stress, overwork	None	Touching, combing hair	Coughing, sneezing, bending	None	Flexing neck, extending legs
Relieving factors	Dark room, rest, sleep	Dark room, rest sleep	None	Rest, sleep	None	None	Standing	None	None
Associated features	Visual, vestibular, or gastrointestinal auras	No aura	Lacrimation, conjunctival injection	Muscle stiffness	Sinus congestion	Malaise, weight loss	Vomiting, blurred vision papilledema	Sudden, abrupt onset	Fever, neck stiffness
Treatment	Ergotamine, methysergide, caffeine	Amitriptyline, beta-blockers, analgesics	Ergotamine, methysergide	Analgesics, anti-inflammatory drugs	Decongestants, analgesics	High-dose steroids	Neurosurgery	Neurosurgical emergency	Intravenous antibiotics

>, Greater than; *M*, male; *F*, female.

TABLE 18-2 CHARACTERISTICS OF FACIAL PAIN SYNDROMES

	TRIGEMINAL NEURALGIA	HERPETIC NEURALGIA	FACIAL MIGRAINE	DENTAL ORIGIN
Age at onset	Over 50	Elderly	Any age	Any age
Gender	F>M	F>M	M>F	Both
Quality of pain	Burning, tingling	Continuous burning	Pulsatile, throbbing	Aching, soreness
Location of pain	Unilateral, one branch of CN V	Unilateral, one branch of CN V	Anywhere on face	Radiating from jaw
Temporal pattern	Sporadic, isolated attacks	Continuous	Sporadic, isolated attacks	Continuous, worse when chewing
Aggravating factors	Hot/cold, facial movement	Touch, cold	Alcohol	Chewing, yawning, pressure
Treatment	Carbamazepine, phenytoin, clonazepam	Analgesics	Ergotamine, methysergide	Bite correction, dental surgery

>, Greater than; *M,* male; *F,* female; *CN V,* cranial nerve V.

include sinusitis, migraine, cluster headache, tension headache, and temporomandibular joint syndrome.

Migraine Headache

Characteristics

Migraine headaches are so varied among patients that this entire class of head pain defies any typical description. In general, migraine occurs on one side of the head and is episodic, with chronic recurrences. Patients often describe ocular or retrobulbar pain, and a visual disturbance is typically associated with migraine. Patients may complain of associated nausea, vomiting, and even diarrhea concurrent with a migraine attack. Patients have reported episodes of syncope related to the onset of a migraine. The onset of migraine can be quite excruciating and is typically unilateral and pulsatile. Patients may report nausea, vomiting, and photophobia.

Epidemiology

Of the U.S. population, 10% has been diagnosed with migraine headache, and it is the most common of all headaches. Of all patients with migraine, three quarters are women, and one quarter report that their first headache occurred before the age of 10 years. The peak incidence of migraine is in patients aged 25 to 55, but first-time occurrence is rare in patients older than age 45. A strong history of migraine exists in the family of most patients, but twin studies show that only approximately one half of these siblings share migraine headache. Therefore, environmental influences are significant factors in precipitating migraine headache.

Precipitating Factors

A litany of known factors can precipitate a migraine attack. These factors include tension, stress, menses, and bright lights. Foods that contain tyramine, such as cheese, meat, and bacon, can precipitate migraine. Of particular concern is the association between migraine and the use of oral contraceptives or nitrates. An as yet unexplained relationship exists between the use of these drugs in migraineurs and stroke.

Pathophysiology

The migraine patient often experiences a prodrome of signs that lead up to a migraine attack. The prodrome, unlike the aura, may occur hours to days before the onset of the attack, and is characterized by altered feelings of mood, including elation or dread. During this time there may be distinct changes in diet, including anorexia or cravings. After this prodrome, the aura may ensue in approximately one quarter of migraine patients. This phase is characterized by scintillating scotoma and metamorphopsia, both of which herald an impending episode of migraine. Regional blood flow studies have demonstrated that during a migraine a reduction in blood flow occurs that starts in the occipital lobe. During this phase the migraine "aura" manifests as visual disturbances and alterations. Other symptoms of the aura include paresthesias, motor weakness, and hearing disturbances. Next, during the "headache" phase, a pounding headache ensues as blood flow increases to the cortex. The headache may last for hours to a full day.

Biochemical changes occur during a migraine attack and mostly involve the depletion of serotonin. An as yet undiscovered disorder appears to exist that causes a central depletion of serotonin-mediated neurotransmission. In addition, reduced magnesium levels and elevated lactic acid levels exist in the brain during the prodrome. Eventually, a wave of depolarization spreads through the cortex and stimulates the trigeminal nerve to release serotonin. The vasoconstrictive effect of serotonin may exacerbate the aura. The actual headache phase is preceded by the release

of neuropeptides that are inflammatory to the meningeal arteries. Inflammation of these neurosensitive blood vessels may cause the headache phase.

After the attack, the migraineur may be irritable and forgetful for a period of several days, known as the postdrome.

Diagnosis

Migraine headache is a diagnosis of exclusion. The neurologic workup is guided by the classic signs and symptoms of migraine headache. Other more life-threatening entities, however, such as stroke, aneurysm, and intracranial tumor must be excluded.

Classification

Classic migraine occurs with an aura and these patients are often seen for eye evaluations to exclude ocular causes of the associated visual alterations. Patients with common migraine do not experience aura and typically are seen first by their primary care physician.

Migraine Headache with Aura

The aura precedes the onset of headache in patients with classic migraine. The patient at first notices a small blind spot, usually just lateral to the point of fixation. This is a positive scotoma because the patient is aware of the presence of missing vision. The area of visual obscuration begins to expand slowly, and within minutes it can encompass much of the visual field. Described as a "scintillating scotoma" or "fortification spectra," the area of visual involvement appears to flicker between blue and yellow. Many patients describe the phenomenon as an area of visual "shimmering" which by description closely resembles the peripheral flashes of light that herald a retinal detachment. For this reason, all patients who complain of what sounds like a scintillating scotoma must have a dilated fundus evaluation to exclude retinal involvement.

The visual aura persists for an average of 20 minutes, although some may last for hours. Although unusual, some patients may experience stroke-like symptomology during an aura or the headache phase, and complain of vertigo, loss of speech, dizziness, hemiparesis, and altered consciousness. In fact, for first-time migraine sufferers a real fear exists that they are having a stroke. However, stroke causes immediate symptomology, whereas neurologic deficits from migraine are characterized by a gradual onset and an eventual and spontaneous resolution.

Migraine Headache without Aura

The migraine without aura, or common migraine, is also distinguished from classic migraine by its bilaterality. It is more common than classic migraine, and can mimic temporal arteritis by causing scalp pain.

Treatment

The first step in the treatment of a confirmed migraine attack is the use of an analgesic such as aspirin, acetaminophen, or naproxen. If this treatment is not effective, the next recommended medication is sumatriptan. This drug is a 5-hydroxytryptamine agonist. Either medication must be taken at the onset of symptoms to be effective.

Prophylactic treatment of recurrent migraine should be considered if the attacks occur more than once per week. Beta-blockers such as propranolol are effective but must be avoided in patients with asthma, congestive heart failure, or insulin-dependent diabetes. In addition, beta-blockers may cause depression and impotence.

The tricyclic antidepressant amitriptyline is also effective but must be avoided in patients with glaucoma. Valproic acid, one of the anticonvulsants, may cause nausea and must be avoided in pregnant migraineurs. Verapamil is a calcium channel blocker that is effective in migraine prophylaxis, but may cause heart problems and constipation. The ergot alkyloids, such as cafergot (ergotamine/caffeine) are effective against migraine but may cause nausea and vomiting.

Cluster Headache

Characteristics

Like migraine, cluster headache typically occurs unilaterally. However, virtually every other characteristic is unlike migraine with or without aura. The headaches, as the name implies, occur in clusters, with a single cluster lasting weeks to months. In between cluster attacks there may be no headache symptomology for months to years before recurrence. A single cluster headache is very brief. They are, in fact, much shorter in duration than migraine headache, and last for minutes to, at most, 2 hours. The cluster headache is constant and nonthrobbing, whereas migraines typically vary in intensity and are often described as pulsatile. The headache most often occurs as night and may wake the patient. It is one of the most painful headaches a patient can experience. During an attack, unilateral conjunctival injection and tearing on the involved side may be present. In addition, a Horner's syndrome may be noted with the miosis and ptosis also on the involved side. A concurrent symptom that complicates the differential diagnosis is the occasional presence of a bulging and pulsatile temporal artery, mimicking an attack of temporal arteritis.

Epidemiology

Cluster headaches occur later in life than migraine, with a mean patient age at onset of 25 years. They occur most often in men, and the most common body

habitus is best described as strong and muscular. Typically there is no family history of headache as in migraine.

Precipitating Factors

Attacks may be precipitated by the ingestion of alcohol or vasodilating medications.

Pathophysiology

The underlying mechanism of cluster headache appears to involve stimulation of the parasympathetic nervous system and the trigeminal vascular system.

Diagnosis

The condition is a diagnosis of exclusion in a patient exhibiting the classic signs and symptoms of cluster headache.

Treatment

Treatment of cluster headache necessitates the use of sumatriptan at the onset of the attack. This serves to mitigate the acute pain and prevent recurrence. Oral indomethacin three times daily is also an effective treatment of the acute attack. Prophylaxis of cluster headache is similar to migraine, with the use of calcium-channel blockers, ergotamine, or 5-HT agonists the medications of choice. The most common prophylaxis medication for cluster headache is verapamil sustained release, a calcium-channel antagonist. This drug is contraindicated in certain heart diseases and can cause constipation. Prednisone or lithium given at the onset of the headache have been shown to improve the headache and prevent recurrence.

Tension-Type Headache

Characteristics

If the presenting symptoms do not match those of migraine or cluster headache, the most likely diagnosis is tension-type headache. The most common presenting clinical picture is a bilateral, nonthrobbing headache that occurs on a nearly daily basis. The most common time of presentation is in the early morning and in the late afternoon. The most common location is the occipital lobe. Simultaneous symptoms such as nausea or aura are usually not present. Patients complain of a feeling as if a tight band is squeezing their head from the occipital lobe, around the neck, and forward to the forehead. The headache will last less than 7 days.

Epidemiology

The first episode of this headache typically occurs in patients older than 20 years and is more common in women. It occurs nearly as frequently as migraine, and some studies show that it is the most frequent of all headache types.

Precipitating Factors

Tension-type headache is not aggravated by routine physical activity.

Pathophysiology

The underlying mechanism is unknown. It is doubtful that stress is the primary cause, although preexisting depression, anxiety, and psychosocial stress, are noted in many cases. During the headache, the scalp and neck muscles are seen to contract, but this is most likely a secondary effect.

Diagnosis

Tension-type headache is diagnosed when migraine, cluster headache, and other primary cranial pathology is excluded.

Treatment

The treatment of tension-type headache is best achieved with aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, or ergotamine. Amitriptyline and propranolol are both useful in the prophylactic prevention of further attacks.

Sinusitis

Characteristics

Sinusitis should be suspected in patients who are seen with head pain isolated to the frontal or maxillary sinuses. These regions are periorbital, thus this headache type is often evaluated in the optometric setting. The head pain is a deep boring uncomfortable feeling in the area of the sinuses around the eyes.

Pathophysiology

The headache is the result of nasal sinus infection.

Diagnosis

Exacerbation of this type of headache is achieved by asking the patient to cough, sneeze, or bend over.

Treatment

Treatment of sinusitis is best achieved with vasoconstrictor agents, although active bacterial infection mandates a systemic antibiotic agent.

Temporomandibular Joint Syndrome

Characteristics

Temporomandibular joint syndrome (TMJ) causes facial pain around the ears. Patients note that when chewing, pain of the jaw muscles, a limitation in jaw movement, and a discernable clicking noise when masticating are present. In addition, the muscles of mastication are tender to palpation. The patient may report a history of

teeth grinding during sleep. Jaw exercises, the local application of heat and the use of a nocturnal bite guard help reduce TMJ jaw pain. In addition, the associated headache can be relieved by the use of NSAIDs.

SECONDARY SUBACUTE HEADACHE

The new onset of headache is an ominous sign of a serious underlying systemic condition or an intracranial disorder. These headaches require immediate evaluation. The subacute headache evolves during a period of weeks and is worrisome particularly if the pain is progressive. Concurrent symptoms such as fever, malaise, lymphadenopathy, stiff neck, or weight loss should prompt an immediate referral to the primary care physician.

Giant Cell Arteritis

Characteristics

Giant cell arteritis (GCA) is characterized by a unilateral or bilateral head pain located in the scalp overlying the temporal artery. The pain is typically a mild-to-moderate boring sensation, and is exacerbated by palpation of the temples when combing the hair or when chewing. Vision loss of the involved eye is the result of inflammation in the arterial wall of the ophthalmic artery. The vision loss can be quite sudden, and some patients wake up to find unilateral blindness, but in other cases the loss of vision can take up to a month to evolve.

Epidemiology

Women are affected more commonly than men and the condition rarely occurs in patients younger than 50 years. Half of all untreated patients go blind in the involved eye. Of all untreated patients, 50% with unilateral blindness as the result of GCA go on to bilateral blindness, sometimes within days.

Precipitating Factors

Age is the single most significant precipitating risk factor in the development of GCA.

Pathophysiology

In GCA an underlying granulomatous arteritis with lymphocytic, neutrophilic, and giant cell infiltration exists in the walls of the mid-to-large sized arteries of the body. The most common vessel affected is the superficial temporal artery (the reason this condition is also known as temporal arteritis), a branch of the external carotid artery, and the vertebral artery. Pain is produced by the inflammation in the artery wall.

Diagnosis

In a patient with sudden, unilateral vision loss with a relative afferent papillary defect and an altitudinal visual field defect in the involved eye, ophthalmoscopy will reveal a swollen, hemorrhagic optic disc with blurry margins. Palpation of the scalp will often reveal a thickened, tender temporal artery. The Westergren erythrocyte sedimentation rate (ESR) is elevated to approximately 100 mm/hr in GCA, whereas in the normal, elderly population it should be no higher than 40 mm/hr. C-reactive protein is also elevated, indicating the presence of an inflammatory condition. A prompt biopsy of the artery will reveal vasculitis characterized by an obliteration of the lumen and infiltration of the vessel wall with lymphocytes, plasma cells, and giant cells. A CBC will reveal the presence of a hypochromic anemia.

Treatment

The goal of treatment is the avoidance of vision loss, although GCA has significant systemic ramifications, because it is a generalized vascular inflammatory condition. Treatment will not restore vision loss in the involved eye; however, the risk of bilateral vision loss is reduced by the initiation of prompt therapy. Clinical presentation along with an elevated ESR is grounds for beginning immediate therapy with intravenous methylprednisolone (500 to 1000 mg every 12 hours for 2 days), or, more commonly, prednisone, 40 to 60 mg/d orally. The headache usually resolves within days. The oral steroid is continued for 1 to 2 months before tapering. Therapy should not be delayed while waiting for biopsy results. The dosage is tapered during a 1- to 2-year period and the effectiveness of therapy is monitored by regular evaluations of the ESR.

Intracranial Mass

Characteristics

Brain tumors often produce head pain that is mild–to-moderate, dull, steady, and intermittent. Associated nausea and vomiting may be present. Mass-related headache is worse when arising in the morning.

Epidemiology

In low-grade gliomas, the majority of patients are seen with seizure activity, while 40% are seen with headache. In malignant glioma, the majority of patients are seen with altered mental status and half of these patients are seen with headache. In benign meningioma, 40% of patients are seen with seizure and nearly the same amount are seen with headache.

Precipitating Factors

The head pain associated with brain tumors is aggravated by a change in head position. Any valsalva maneuver, such as coughing, sneezing, or orgasm, will worsen a tumor-related headache.

Pathophysiology

Intracranial masses comprise the entities of brain tumor, subdural hematoma, aneurysm, or abcess. Headache is produced by compression, distortion, displacement, or inflammation of pain-sensitive structures by the mass lesion. Any increase in intracranial pressure (ICP), such as from coughing or sneezing, will worsen a cranial mass-related headache.

Diagnosis

In the optometry office, a new onset of subacute head pain should initiate an immediate evaluation of extraocular muscle movements and a papillary evaluation. After recording pupils, a dilated fundus evaluation is necessary to exclude papilledema or swelling of the optic nerve head. During the time it takes to dilate the patient, it is recommended that the patient have visual fields performed to exclude visual field defects. Any suspicion of an intracranial mass warrants an immediate evaluation with computed tomography (CT) scan or magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA). Referral through the primary care physician is usually made to neurology.

Treatment

Treatment of brain tumor is dependent on type and location.

Trigeminal Neuralgia

Characteristics

Trigeminal neuralgia, or tic douloureux, is characterized by unilateral facial pain distributed along the second and third divisions of the trigeminal nerve. The headache is characterized by sudden, quick jolts of excruciating episodes of pain that exacerbate and remit spontaneously. The condition is considered by Gutrecht and Tarlov as one of the worst pains that humans experience. The condition rarely occurs during sleep.

Epidemiology

The condition typically develops in mid to late life.

Precipitating Factors

Trigger zones exist that, when stimulated, precipitate the onset of the pain. The areas stimulated by touch include the cheek, mouth, and nose. In addition, shaving and chewing may initiate trigeminal neuralgia. Cases have been reported to occur after exposure to cold temperatures or wind on the face.

Pathophysiology

Trigeminal neuralgia is of unknown cause. In this condition, the trigeminal nerve roots are proximal to a vascular structure lengthened and made tortuous by age, and microvascular compression of the nerve is thought to contribute to the induced head pain. In addition, some believe that a loss of myelin insulation of the posterior trigeminal nerve contributes to the condition.

Diagnosis

Neurologic testing and imaging is all negative, although the presenting symptoms should be differentiated from MS and brain tumor.

Treatment

The treatment of choice is carbamazepine, 400 to 1200 mg/d orally in three divided doses. This medication raises the threshold of pain by stabilizing cell membranes. Relief of the pain occurs in 24 hours. Abortion of an acute attack may be achieved by intravenous phenytoin, 250 mg. In extreme cases that are resistant to medication, the surgery of choice is posterior fossa microvascular decompression.

SECONDARY ACUTE HEADACHE

Patients with the classic acute headache are seen with the complaint of the head pain being " . . . the worst I have ever had in my life!" These patients are often brought to the emergency room and so rarely are seen by the optometrist. Any "first and worse," or head pain associated with neck stiffness must be evaluated immediately. The most common cause of life-threatening acute, excruciating headache is subarachnoid hemorrhage. Head pain associated with neck stiffness and fever mandates an evaluation for meningitis. Two primary sources of bleeding can contribute to a subarachnoid hemorrhage: a burst aneurysm or bleeding of a nonaneurysmal structure, the arteriovenous malformation (AVM).

Subarachnoid Hemorrhage

Characteristics

The hallmark sign of subarachnoid hemorrhage is the sudden and spontaneous onset of a severe, unbearable, and generalized global headache. This condition does not occur without head pain. Syncope, nausea, and vomiting at the outset of the headache are common. Coincident with the hemorrhage is a rise in blood pressure and a fever. The conscious patient may experience altered cognitive behavior. The unconscious patient may fall into a coma.

Epidemiology

A cerebral artery aneurysm rupture occurs most frequently in the fifth and sixth decades. It occurs in males and females equally. AV malformation aneurysms occur twice as often in men as in women and these tend to rupture between the ages of 20 to 40 years. In the

United States 28,000 cases of ruptured intracranial hemorrhage occur per year. Of patients with subarachnoid hemorrhage, 20% die before reaching hospital. Of those that reach hospital, one quarter die from the hemorrhage within 2 weeks. Another 25% die from a second bleed of the aneurysm if not surgically corrected. Of all survivors of subarachnoid hemorrhage, half have irreversible brain damage. AVMs have a much better prognosis, because 90% of these patients recover with no surgical intervention.

Precipitating Factors

Increasing age and the location of the aneurysm are significant factors in the development of subarachnoid hemorrhage. Systemic hypertension has not been correlated to the formation of the aneurysm, but the sudden elevation of blood pressure at orgasm has been reported as increasing the risk of aneurysmal rupture. Other risk factors associated with ruptured aneurysm include smoking, alcohol consumption, and the use of oral contraceptives.

Pathophysiology

This headache is caused by a spontaneous and nontraumatic hemorrhage into the subarachnoid space, the area located beneath the arachnoid coverings of the brain. The source of the bleed is most commonly a ruptured aneurysm, which are spherical outpouchings representing weaknesses in the blood vessel wall. Hemodynamic stress placed on an area of structural weakness within the aneurysmal wall causes the rupture. Of intracranial aneurysms, 85% are associated with the anterior circulation, and only 15% arise from the posterior circulation.

Of all subarachnoid hemorrhages, three quarters are the result of a berry aneurysm. Most cerebral artery aneurysms are berry aneurysms, which are congenital in nature and develop from a weakness in the vessel wall. The most common site of the berry aneurysm is the area of vessel branching around the circle of Willis.

AV malformations allow blood to flow from an artery to a vein without passing through a capillary bed. The intervening vessel, known as an AVM, is susceptible to aneurysm. Most AVMs arise around the area of the middle cerebral artery.

When an intracranial artery ruptures, an immediate outpouring of blood occurs from the vessel into the subarachnoid space. This increases ICP, causing distortion of pain-sensitive intracranial structures. In addition, cerebral blood flow decreases, leading to syncope in half of the patients.

Diagnosis

Ophthalmoscopy may reveal subhyaloid preretinal hemorrhages that are the result of a rapid elevation in ICP. These are virtually pathognomonic of subarachnoid hemorrhage but occur in only 20% of cases. Terson's syndrome, in which a burst aneurysm from the anterior circulation causes hemorrhage into the vitreous cavity, may cause visual loss, and in some cases require a vitrectomy.

Extraocular muscle involvement may help to localize the location of the aneurysm. Abducens palsy resulting in an esotropic posture may occur from an intracavernous carotid aneurysm. Oculomotor palsy with unilateral ptosis and mydriasis in an eye that is "down and out" is a frequent complication of carotid-posterior communication aneurysms.

Visual field findings may help determine the location of the aneurysm. A bitemporal hemianopsia, denser above, is typical of a supraclinoid carotid aneurysm extending superiorly and pressing on the optic chiasm from below. Compression of the optic chiasm from above results in a bitemporal hemianopsia that is denser below.

CT scan should be performed within 24 hours of the onset of headache and will reveal areas of high density representing blood in the subarachnoid space near the circle of Willis. AVMs will be detectable on CT scan with contrast or MRI. A lumbar puncture will reveal elevated opening pressure with bloody fluid.

Treatment

The goal of medical treatment of subarachnoid hemorrhage is the prevention of rebleeding. Bed rest with elevated head position at 20 degrees with mild sedation will help reduce the recurrence of hemorrhage. Analgesics are given to alleviate the head pain, but aspirin must be avoided as it may promote rebleeding. Adequate blood pressure control reduces the mortality associated with subarachnoid hemorrhage. Nimodipine, a calcium channel antagonist, is given to reduce the ischemia of cerebral vasospasm.

The surgical goal of a ruptured aneurysm is an improved clinical outcome. This can be accomplished by two techniques. The first involves clipping the neck of the aneurysm. The second places a coil within the artery to induce clotting. The surgical intervention of an AVM is not as urgent as with aneurysm and involves the resection of the entire AVM if it is surgically accessible, or the ligation of feeding blood vessels.

Complications of subarachnoid hemorrhage include rebleeding, hemiparesis, aphasia, hydrocephalus, seizures, and diabetes.

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CHAPTER 19

Mental Health

CHAPTER OUTLINE

States of confusion may be acute or chronic in patients with mental health disorders. Acute confusional states, also known as "change in mental status" or "delta MS," differ greatly from chronic psychiatric disorders. The true confusional state is acute in onset, often with an onset of seconds to hours, and is the result of such causes as drug intoxication, endocrine disorders, head trauma, seizures, and infection. Psychiatric disorders are characterized by long-term confusional states of cognitive awareness. The true psychiatric disorder

may take weeks to months to develop and is often the result of a primary brain disease such as Alzheimer's disease, dementia, bipolar disorder, and depression.

The characteristics of confusional states and psychiatric disorders are similar. Patients will be easily distracted and may appear agitated. Cognitive powers are reduced and the patient may be incoherent or even delusional. In both acute and chronic confusion hallucinations may be present.

Psychiatric disease includes mood, psychotic, and anxiety disorders. Mood disorders include depression and bipolar disorder. Psychotic disorders include schizophrenia and delusion disorder. Anxiety disorders includes posttraumatic stress syndrome.

Psychiatric disorders often produce disorientation to the point of cognitive impairment, but the patient has a normal level of consciousness. Often the patient is not consistently oriented to time, place, and person. Characteristics of psychiatric disease include disturbed thoughts and abnormalities in perception. Often the patient with mental disease displays inappropriate behavior. Personality changes are noted by family members and friends.

DEMENTIA

Characteristics

Dementia is characterized by an impairment of cognitive function with no effect on consciousness. Dementia rarely causes sleepiness, inattention, or disorientation until late in the disease.

Epidemiology

Dementia affects as many as one fifth of all individuals older than 65 years. The greatest risk factor for dementia is age. Approximately 4 million cases of dementia are caused by Alzheimer's disease.

Pathophysiology

The underlying pathology is an acquired, progressive, and generalized abnormality within the cerebral cortex and its subcortical connections. The most common causes of dementia are, in order of frequency, Alzheimer's disease, Parkinson's disease, and multiinfarct dementia.

Diagnosis

The diagnosis of dementia is challenging and problematic. No specific screening tests, laboratory tests, or any imaging tests exist that can confirm the diagnosis. The complaint of memory loss is nonspecific because it is so common in the elderly population. For instance, only one tenth of elderly patients who complain of memory loss actually go on to develop dementia. However, more than half of all elderly patients who develop dementia never complain of memory loss.

Cognitive testing in suspected dementia cases reveals minor changes in neurologic function and reduced short-term memory capacity.

The ocular examination in dementia patients is critical in determining the etiology of the disorder. A dementia patient with a Kayser-Fleischer ring should have an evaluation for Wilson's disease. The finding of papilledema may indicate that the dementia is related to a cranial space-occupying lesion such as a brain tumor. The presence of pinpoint pupils is most suggestive of dementia from neurosyphilis. A dementia patient with ophthalmoplegia should be evaluated for progressive supranuclear palsy.

Neuroimaging will reveal enlargement of the ventricles and cerebral cortical sulci.

Differential Diagnosis

Alzheimer's Disease

The most common cause of dementia, Alzheimer's disease is characterized by a progressive degeneration of the brain that results in impaired memory and disorientation.

The incidence of Alzheimer's disease peaks in patients between the ages of 65 and 85 years. Half of the population older than 85 years is afflicted with Alzheimer's disease, and more than 20 million cases of Alzheimer's disease exist throughout the world. Age is the leading risk factor, although genetic susceptibility to the disease plays a role in approximately 5% of cases. Women are at greater risk of developing Alzheimer's disease than men. In addition, patients with a history of head injury or exposure to toxins or free radicals are predisposed to the development of the disease. Patients with hypertension or a history of stroke are also at greater risk for developing Alzheimer's.

Alzheimer's disease results from an elevated level of beta amyloid in the brain. This protein is inappropriately deposited in neural tissue and is toxic to brain synapses and neurons. The brain damage is characterized by the presence of "plaques and tangles." Neuritic, or senile, plaques represent the extracellular deposition of several types of proteins. These proteins are also deposited abnormally in the cerebral and meningeal blood vessels. Tangles represent the intracellular deposition of abnormal protein. The disease worsens as the number of neurofibrillary tangles increases.

The brain damage begins in the hippocampus and spreads to the subcortical gray matter of the temporal lobe (causing "naming impairment"), parietal lobes, and frontal lobe (causing global aphasia). The last area to become involved is typically the occipital lobe.

The earliest manifestations of Alzheimer's disease are short-term memory loss and disorientation to time and place (Box 19-1). In Alzheimer's disease the loss of neurons in the hippocampus is thought to disconnect the memory processing area from two significant areas: the memory storage area in the neocortex, and the input area for new sensory information. The patient may experience forgetfulness, leading to mismanagement of medications, failure to pay bills, cooking disasters, and driving accidents.

Depression also often characterizes the early stage of Alzheimer's, and results from subcortical, cortical, and limbic neuron dysfunction or loss. As a result of this neuronal pathology, a reduction in the level of neurotransmitters occurs, with a subsequent propensity towards depression.

As Alzheimer's disease progresses, the patient may become agitated and restless. Typically, incidents occur in which the patient wanders away from familiar surroundings only to become lost because of a visuospatial disturbance. There may also be significant language impairment, displayed as word-impairment, name-impairment, and a loss of comprehension.

In time the patient may exhibit socially inappropriate behavior. Dressing and personal hygiene become nearly impossible. Cognitive abnormalities occur, including psychosis, delusions, paranoia, and hallucinations.

In the advanced stages of Alzheimer's disease, the patient may experience loss of bowel and bladder control with the necessity of nursing home care. Death usually occurs within 10 years of the onset of the disease and is most commonly the result of aspiration pneumonia.

The diagnosis of Alzheimer's disease is difficult, particularly in its earliest stages. In testing patients who may have Alzheimer's, significant suspicion is raised when an individual cannot recall information despite repetitive practice. In addition, Alzheimer's patients have difficulty listing items in a single category within a minute's time.

The treatment of Alzheimer's disease with medication produces some improvement in moderate-to-severe disease. The *N*-methyl-D-aspartate (NMDA)-type glutamate receptor antagonist drug memantine has been shown to modestly improve the symptoms of Alzheimer's disease, especially when combined with cholinesterase inhibitors.

Incremental improvement in the disease is also found by administration of acetylcholinesterase inhibitors, such as donepezil, galantamine, physostigmine and tacrine. These drugs prevent hydrolysis of acetylcholine and increase the cholinergic action from the basal forebrain to frontal cortex, amygdala, and hippocampus. Use of these drugs has been shown to have a small effect on cognitive function. The drug of choice in the United States is donepezil, mainly because it has fewer side effects than the other medications.

Present research into the treatment of Alzheimer's disease is focusing on vaccines that prevent abnormal protein deposition in the brain.

BOX 19-1
SIGNS AND SYMPTOMS OF POSTERIOR CORTICAL ATROPHY (VISUAL-SPATIAL FORMS OF ALZHEIMER'S DISEASE)

Complaints: Blurred vision, reading difficulty, difficulty walking up and down stairs and inclines, difficulty reaching for objects, confusion when presented with an array of objects, objects "pop in and out of view."
Acuity: rarely completely normal, usually approximately 20/30 until the disease is far advanced.
Visual fields: Testing is labored and inconsistent, especially to multiple simultaneous stimuli. Formal kinetic testing usually reveals constricted fields. Automated static testing is hopeless as a result of impersistence and inattention.
Color vision to plain squares is normal. The patient is unable to perform the Ishihara test because of visual-spatial inability.
Ocular apraxia: Visually guided saccades and pursuit movements are abnormal. Saccades to nonvisual commands are slowly initiated. Random saccades are of normal amplitude and velocity.
Optic ataxia: misreaching for external targets (such as the examiner's fingertip). Reaching for the patient's own clothing or body parts (under somesthetic guidance) is normal.
Bilateral visual inattention: spotty piecemeal performance on line cancellation test.
Simultanagnosia: Identification of pictures of single objects is relatively preserved; performance on complex scenes or pictures of multiple objects is dramatically poorer.
Visual memory for familiar or famous faces is intact, although testing may be difficult because of inability to fix gaze.

Pick's Disease

Similar to Alzheimer's disease, this form of dementia begins earlier in life with profound behavioral dysfunction. Patient age at onset is between 21 to 75 years, but usually between 45 to 60 years. The average duration of the disease from onset to demise is usually 8 years.

The typical onset is heralded by a quick demise in social and personal behaviors. Pronounced changes in affect occur, with patients exhibiting overexcitement, cognitive disorganization, apathy, and behavioral rigidity.

The computed tomography (CT) scan or magnetic resonance imaging (MRI) scan demonstrates atrophy of the frontal and anterior temporal lobes. For this reason, Pick's disease is also known as frontotemporal dementia (FTD), or Pick's complex. The superficial

layers of the involved lobes become gliotic and are characterized by neuronal dysfunction and destruction. It is differentiated from Alzheimer's disease only on autopsy. No known treatment for this form of dementia exists, and sedatives are often given by caregivers in an effort to quell combative and aggressive behavior. Selective serotonin reuptake inhibitors (SSRIs) are of limited effectiveness in reducing anxiety or depression related to Pick's disease.

Creutzfeldt-Jakob Disease

This form of dementia is transmissible and precautions must be taken to prevent infection. Also known as transmissible spongiform encephalopathy (TSE), Creutzfeldt-Jakob disease (CJD) is a sporadic human form of the disease. Because this is a naturally acquired disease, the patient age for this form of dementia ranges from ages 16 to 82 years.

An infectious agent is passed from animal to human to cause this disease. The agent is a protein known as a prion. Prion proteins accumulate in the brain, as well as other organs including the eyes, lungs, kidneys, spinal cord, and lymph nodes. The disease progresses from mild dementia to coma in a few months. Rare visual field defects and extraocular muscle palsies are associated with this condition.

A variant of Creutzfeldt-Jakob disease is "mad cow disease," or bovine spongiform encephalopathy. This infection is transmitted by ingestion of infected meat. The incubation period can last for decades. In this condition, the onset of dementia occurs at approximately 30 years of age, with the earliest symptoms being intellectual impairment and personality disturbances. Eventually, parkinsonism develops with weakness and loss of motor control. MRI is becoming useful in the diagnosis of CJD and is revealing bright lesions in the pulvinar.

End-stage CJD occurs within 1 year of the onset of dementia as the patient becomes comatose. Most patients die within 5 to 12 months. Autopsy reveals the presence of cerebral plaques.

No treatment exists for CJD.

Dementia in Systemic Disease

Dementia may arise in many systemic conditions, including brain tumor, AIDS, syphilis, and alcoholism.

Dementia can often be caused by brain tumors, most commonly frontal or temporal lobe gliomas.

Dementia is often associated with AIDS as the retrovirus invades the central nervous system. Infection with HIV-1 may produce an acute confusional state because of stroke, seizure, lymphoma, meningitis, encephalitis, cerebral toxoplasmosis, or metabolic disorders.

In neurosyphilis, or lues, dementia occurs no earlier than 2 to 12 months after infection. Syphilis is called by the spiral bacterium *Treponema pallidum*. Approximately one fifth of all syphilis patients go on to develop neurosyphilis, wherein chronic granulomatous inflammation affects the central nervous system (CNS) tissues.

Shortly after the initial infection and coinciding with the syphilitic rash, syphilitic meningitis will cause headache, fever, a stiff neck, and cranial nerve palsies.

Within a decade of untreated syphilis, neurological manifestations may include transient ischemic attacks (TIAs) and stroke as part of meningovascular syphilis. These neurologic disorders are the result of brain infarction from the chronic inflammation. Ocular manifestations of neurosyphilis include Argyll Robertson pupils, optic atrophy, ptosis, and ophthalmoplegia.

Tabes dorsalis, now a rare complication of neurosyphilis, is characterized by unsteadiness, incontinence, and excruciating abdominal pain. It is caused by spirochetic invasion of the posterior nerve root fibers of the spinal cord, optic nerves, and oculomotor nuclei. Additionally, the subsequent immune response in these tissues causes further neuronal destruction, leading to optic atrophy, urinary disturbance, and gastric crisis. If general paresis is present, the condition is known as taboparesis.

The treatment of syphilis at any stage is penicillin.

Alcoholism can possibly produce dementia by the direct toxic effect of ethanol on neurons in the brain. More likely, dementia may occur because of nutritional deficiency associated with alcoholism. For example, the condition of pellagra, which causes optic atrophy and dementia, is the result of a deficiency of niacin.

Treatment

The treatment of dementia remains problematic because only approximately 10% of dementia cases are reversible. Through appropriate management, dementia may be halted and the quality of life improved for many patients.

DELIRIUM

Characteristics

Delirium is characterized by an acute onset of cognitive dysfunction, impaired consciousness, a reduced state of arousal, and delusions. The onset of symptoms may occur within hours, and symptoms are usually worse at night. At first, poor concentration and a reduced attention span are experienced, with sudden loss of short-term memory. The patient may become confused and drowsy, and eventually fall into a stupor. Depression and anxiety may result from delirium. In time, delusions and hallucinations may occur.

Epidemiology

The elderly and postoperative patients are at greatest risk for developing delirium. The most significant risk factors in the development of delirium include social isolation, sensory deprivation, and sudden changes in the environment. Among hospitalized patients, approximately half have some form of delirium, and the rate is as high as 80% in terminally ill individuals.

Pathophysiology

Because of malnourishment, in alcoholism a thiamine deficiency is often present that leads to delirium. In liver disease, an increased level of NH3 is present that causes reduced psychomotor activity.

Precipitating Factors

Delirium may be caused by infectious processes, drug abuse, and alcohol withdrawal.

Delirium tremens, or the "DTs," is caused by the sudden cessation of alcohol in a chronic alcohol abuser. Typical symptoms of the DTs occur 2 to 7 days after withdrawal of alcohol and include fever, severe tremor, dilated pupils, hypertension, and tachycardia. The DTs, or "the shakes" (as they are often referred to by alcoholics), lasts for an average of 3 days. During this time the alcoholic experiences delirium characterized by fever, sweating, confusion, easy agitation, and systemic hypertension. Although the DTs typically resolve within a week, if left untreated, chronic cases may result in coma and death. The mortality associated with the DTs is often the result of infection, pancreatitis, or myocardial infarction.

Other causes of delirium include liver and renal failure, hypoglycemia, infections, head trauma, epilepsy, cancer, and drug use. The most common medications associated with delirium include the sedatives and narcotics. Delirium often occurs 1 to 3 days after sedative drug withdrawal.

Diagnosis

Delirium must be differentiated from dementia. Delirium is typically an acute onset of impaired consciousness that consists of disorientation, psychosis, and motor abnormalities. The onset of dementia is more chronic, with little effect on consciousness, and is characterized by normal orientation, poor memory, normal motor skills, and less prominent psychosis.

Treatment

Delirium tremens, because of sudden alcohol withdrawal, is sometimes treated with benzodiazepine medications. Diazepam is given intravenously until the patient is calm, to reduce morbidity and death associated with the cessation of alchohol. Otherwise, most cases of delirium are short-lived and self-limiting episodes that are treated with supportive measures.

DEPRESSION AND DYSTHYMIA

Characteristics

This chronic and progressive condition results in emotions ranging from extreme sadness to anxiety with a simultaneous loss of enjoyment. In severe cases, patients may become suicidal or psychotic. Psychosis-related depression is characterized by delusions of poverty or life-threatening illness concurrent with physical complaints, in particular bowel dysfunction.

Epidemiology

Of all serious mental health issues, depression is the most common. Second to only cardiovascular disease, depression is a significant cause of work-related sick days and medical-related loss of income. One fifth of the U.S. population has reported at least one episode of major depression. Women have a higher rate of depression and men have a higher incidence of attempted suicide.

Depression usually begins in adolescence and a strong familial trait appears to exist.

Pathophysiology

Subtle endocrine disturbance have been linked to depression. Hypercortisolism has been shown to occur frequently in cases of depression. The cause of depression is unknown. In dementia associated with Parkinson disease, a characteristic histological lesion exists known as a Lewy body. These inclusion bodies are located within the cytoplasm of the neurons of the substantia nigra and are found upon autopsy. The most common cause of depression is Alzheimer's disease. The second most common cause is dementia with Lewy bodies, followed by frontotemporal dementia and vascular dementia.

Precipitating Factors

The medical conditions that most commonly precipitate major depression include thyroid disease, alcohol abuse, and steroid use. The risk factors that most commonly provoke suicide attempts among severely depressed individuals include intense anxiety, advanced age, and alcohol or drug abuse. Suicide is more common among men than women.

Diagnosis

The recognition of depression is often challenging and relies on the recognition of traits that are characteristic of the disorder. The clinician should be sensitive to the

typical signs of depression. These include distorted thinking, feelings of powerlessness, chronic sadness, insomnia, impaired concentration, and thoughts of suicide. These symptoms are typically worse in the morning, and the diurnal fluctuation of mood is characteristic of depression. If psychosis is present, the depressed patient will also exhibit delusions of poverty, medical illness, or moral depravity.

Treatment

The treatment of depression has two goals. The first goal is the therapy that best targets the cognitive dysfunction: psychotherapy. This form of cognitive therapy can modify the pattern of distorted thinking and develop appropriate psychotherapeutic strategies for intervention.

The second goal is the improvement and remission of the mild depressive state that occurs in about half of all cases with the use of an SSRI. These medications have fewer side effects than the tricyclic antidepressants. Alternatives to the SSRIs are lithium and triiodothyronine.

Severe depression responds to electroconvulsive therapy in 90% of cases. This type of therapy is also of use in cases of suicidal tendencies and patients who are too ill to take the appropriate medications.

The treatment for psychosis-related dementia, with such delusions as hypochondria, nonexistent poverty, or religious fanaticism is electroconvulsive therapy, or a combination of antipsychotic and antidepressant medication.

BIPOLAR DISORDER

Characteristics

Bipolar affective disorder is characterized by a personality that constantly switches between mania and depression. The state of mania is characterized by excessive happiness, gregariousness, and scheming. The manic patient constantly talks of plans that concern financial success, often with altruistic overtones. The manic patient energetically schemes to make themselves as well as those around them wealthy, successful, and happy. In this phase the patient is extremely likable, personable and, with the possible exception of the constant and unceasing chattering, engaging.

In the extreme case, however, mania may produce delusional states of grandeur. The manic patient may, for example, declare that they are the "ruler of the world," or that they are "the wealthiest person in the world." In time, insomnia, agitation, and hyperexcitability may occur. Spontaneous aggression may result in unexpected conflicts with innocent bystanders. Interaction with a manic patient, therefore, is often described as "walking on eggshells on top of thin ice."

Nearly all manic patients eventually develop severe depression. These periods are characterized by serious apathy, sadness, loss of motivation, and isolation. In time, the bipolar "switches" occur more frequently and require less external stimulation. The patient with bipolar disorder increasingly requires hospitalizations and must be monitored for alcoholism, drug dependency, and suicide.

Epidemiology

The condition affects men and women equally. Early bipolar affective disorder may begin as childhood depression.

Pathophysiology

The cause of bipolar affective disorder is unknown, although genetic proclivity is firmly established by epidemiological studies.

Precipitating Factors

A strong genetic tendency exists for the disorder, with most patients with bipolar disorder having a relative with the disease. Individuals have a 10% chance of developing bipolar disorder if there is a first-degree relative with the condition.

Diagnosis

Establishment of the condition is based on a careful history. It is essential to gather as much information from relatives and friends to establish the presence of bipolar manifestations. The patient is likely to be a poor historian because of frequent embellishment. Any patient exhibiting depression or elation who has a family member with confirmed bipolar disorder should be strongly suspected of having the condition.

Treatment

Bipolar disorder requires lifelong mood stabilizing medication. The only medication shown to stabilize mood swings and reduce the risk of suicide in bipolar disorder is lithium. There are significant side effects associated with this medication. Other medications used in bipolar disorders are high doses of thyroid medication, anticonvulsants (lamotrigine), and antidepressants. Electroshock therapy is also effective in stabilizing mood. Recently it has been shown that diets high in omega-3 unsaturated fatty acids found in fish reduce relapse rates in bipolar individuals.

SCHIZOPHRENIA

Characteristics

Schizophrenia is characterized by an early onset of psychoses that at first produce unsociable behavior and progress to hallucinations, delusional beliefs, and suicide.

The earliest symptoms typically begin in early adolescence. The young patient will be seen to act strangely, exhibiting odd and eccentric behavior. In time patients will isolate themselves from the public and often talk of hearing voices.

End-stage schizophrenia manifests as an extreme paranoiac state wherein the patient stops caring for him or herself. A loss of reasoning, memory, and abstract thinking is experienced.

Epidemiology

Approximately 1% of the entire population has schizophrenia, and a large proportion of nursing home patients are schizophrenic. One tenth of all schizophrenics commit suicide.

Pathophysiology

The cause of schizophrenia is unknown, and although a genetic vulnerability appears to exist towards developing the disease, identical twin studies reveal that only 50% of these siblings both exhibit the disorder. Thus, with half of all twin pairs having only one sibling with the disorder, the cause is obviously not entirely to the result of environmental factors such as parenting issues. Risk factors appear to be a winter birth, malnutrition of the mother during pregnancy, and an older age of the father. Recent proposals link genetic proclivity (because of mutations) with early environmental influences.

Precipitating Factors

Stress can precipitate an acute outbreak of schizophrenic behavior. Emotional turbulence within the patient's household will often exacerbate hostile behavior. In addition, city dwellers are at greater risk of developing the disease.

Diagnosis

The disorder is diagnosed on the basis of a careful history and psychological evaluation of the patient. Some feel that the diagnosis is automatic if the patient exhibits delusions of thought control. Another diagnostic strategy is to evaluate the patient over time and monitor for the other signs and symptoms of schizophrenia. The MRI or CT scan is useful because it reveals ventricular enlargement, and reduced temporal or frontal lobe size in 50% of cases. The ocular examination of a schizophrenic may reveal abnormal pursuits on extraocular muscle testing.

Treatment

Neuroleptic medications act by blocking dopamine receptors and when given to a schizophrenic patient will often reduce delusions and hallucinations. Unfortunately, these same medications tend to exacerbate social withdrawal and isolation.

OBSESSIVE-COMPULSIVE DISORDER

Characteristics

This condition is the repetition of unwanted and undesirable thoughts or actions that impair everyday functioning. The patient with obsessive-compulsive disorder (OCD) seems unwillingly compelled to repeat the same action for hours at a time and for no logical reason. These patients struggle with their unwanted thoughts or actions, and are truly tormented souls.

Epidemiology

The worldwide prevalence of OCD is about 2%. OCD is more common in males and in first-born children.

Pathophysiology

A genetic proclivity exists towards developing OCD. Excess metabolic activity in the frontal and caudate regions of the brain is present, although the significance of this is as yet unknown. Nonetheless, this finding is seen in almost all patients with OCD. The areas of the brain that are involved appear to be the frontal-subcortical neural circuit.

Precipitating Factors

A core fear triggers anxiety, and the obsessive behavior is initiated to relieve the emotional nervousness.

Diagnosis

A person who repeats an action but does so happily does not have OCD. Manifestations of OCD include those who hand wash constantly because of illogical concerns about germs, constantly check the doors of their house to make sure the locks are secure, or arrange and rearrange personal objects in exactly the same position. Some patients manifest OCD by hoarding "junk," such as newspapers, string, personal possessions, and trash. The patient with OCD often illogically feels that they may cause injury or death to

another person, however, and are tormented by these thoughts.

OCD can be detected by brain abnormalities on positron emission tomography (PET) or functional MRI scans. These patients show excess metabolic activity in certain brain regions. Perfectionism, gamblers, "sex-addicts," and hair-pullers do *not* have OCD, because they manifest none of the structural brain changes seen on neuroimaging.

Treatment

OCD is improved by use of antidepressants that block reuptake of serotonin. Clomipramine, fluoxetine, and fluvoxamine (an SSRI) are the approved medications for treatment of OCD.

PANIC DISORDER

Characteristics

The manifestations of panic disorder include sudden bouts of chest pain, difficulty breathing, profound anxiety, and hyperventilation. The panic episode is of sudden onset and typified by an intense fear that lasts for approximately 1 hour.

Epidemiology

One fifth of all patients who are seen with a chief complaint of syncope are ultimately diagnosed as having panic disorder.

Pathophysiology

It is believed that patients with panic disorder are overly sensitive to small changes in blood PCO_2 and pH. These changes alert the normal individual to increase respiration. In the patient with panic disorder, these same changes cause profound anxiety of suffocation. In a sense, the patient with panic disorder is overly sensitive to the built-in "suffocation alarm" of the body.

There is often a familial tendency in the family towards panic disorder, and a genetic proclivity is likely.

Precipitating Factors

Patients report a sudden recognition of their own physiology and bodily sensations. Self-evaluation of their symptomology produces anxiety of an impending medical emergency. These episodes may last for hours, between which they are in their own typical health. Fear of being isolated and far from help may cause the patient with panic disorder to shun going outside. They may become housebound because of fear of eventual isolation and eventual exacerbation of a panic attack.

When arousal is triggered by rising blood pH and PCO_2, the internal respiration signal is triggered. In the normal patient, this mechanism subconsciously increases respiration. Patients with panic disorder have a heightened state of awareness concerning their somatic status, and the same respiration signal induces an immediate sensation of suffocation, resulting in anxiety, hyperventilation, and a panic attack.

Diagnosis

The differential diagnosis includes asthma, chronic obstructive pulmonary disease (COPD), cardiac arrhythmias, heart attack, caffeine, alcohol, and pheochromocytoma.

Treatment

Patients are educated as to the cause of their panic disorder through appropriate psychological counseling. Pharmacological intervention includes the benzodiazepines that can quickly mitigate an attack.

ATTENTION DEFICIT DISORDER

Characteristics

Attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD), are conditions that primarily affect children and are characterized by distractibility and difficulty in maintaining focus on a subject. Hyperactivity does not have to be present to make the diagnosis of ADD, but energetic behavior with poor self-control is a typical manifestation of ADHD.

Much controversy surrounds the validity and value of the diagnosis of ADD/ADHD, and even more surrounds the medical treatment of this condition. Among educators a strong desire exists to optimize the teaching experience for the teacher, student, and classroom. The appropriate use of medication has been shown to decrease distractibility while improving attention among students with ADD/ADHD. This is of benefit to the teacher because there is less distraction in the classroom and a greater ability for the treated student to assimilate knowledge.

Significant controversy exists, however, concerning the diagnosis and treatment of ADD/ADHD. Great fear exists among some parents that ADD/ADHD is being overdiagnosed in the schools to medicate students. Controversy also surrounds the very nature of the diagnosis of ADD/ADHD.

Epidemiology

A half century ago no children were diagnosed with ADD/ADHD, although some children were easily distracted and hyperactive. These students exhibited

inattentiveness to their work and poor self-control. By 1987, 3% of children had been diagnosed with ADD/ADHD. Now, ADD/ADHD has been diagnosed in 10% of school-age children, or more than two million young individuals, and the prevalence is constantly increasing.

Although this condition has traditionally been thought to occur more in boys than in girls, some studies find this not to be the case. Of the untreated cases, almost all report that hyperactivity improves in adulthood, but half continue to have cognitive disability.

Pathophysiology

The prefrontal cortex, striatum, and cerebellum are seen in imaging studies to become asymmetric and reduced in volume. PET scanning reveals reduced perfusion to the frontal areas of the brain during periods of attempted sustained attention.

Precipitating Factors

This condition appears to be strongly genetic in predisposition.

Diagnosis

Extensive psychological testing is necessary before the diagnosis of ADD/ADHD is made. Even then, in many cases, the diagnosis is not clear cut, and parents may eventually have their child tested by several different specialists. Left untreated, these children are at great risk for alcohol and drug abuse, dysfunctional behavior, and failure in school.

Treatment

Inappropriate medicating of the patient must be avoided. To this end, appropriate diagnosis is mandatory. Once the parent, child, and doctor are all committed to treatment, then the use of stimulant medication is presently considered appropriate and effective by some, but not all, specialists.

Ritalin (methylphenidate hydrochloride) is an amphetamine-like drug approved in 1955 by the Food and Drug Administration (FDA) for use in controlling mild depression in adults. Ritalin reduces motor movements and increases attentiveness in task-oriented settings. It has been shown to reduce aggressive behavior and improves short-term memory in children. Improvements have been documented in reading comprehension, memory and writing tasks. Parents and teachers have repeatedly cited Ritalin as having a positive effect on mood, concentration, focus, and self-image. The long-term effects of Ritalin on these children are as yet not established and not documented.

Ritalin has some significant risks that have raised a storm of controversy. For example, it is a Schedule II drug, meaning that it has the highest potential for abuse. In addition, there are significant side effects, including nervousness, anorexia, insomnia, gastrointestinal complaints, and dizziness. These side effects usually disappear in time and with dosage adjustment.

Ritalin may make the child more socially isolated. Anecdotal reports exist of a loss of creativity in patients taking Ritalin. Although it reduces aggressive and distracting outbursts, it often produces a withdrawn, unmotivated personality. Some parents have complained of a loss of a "spark" that seemed the very life of their child's personality. On the other hand, the same parents often credit the use of Ritalin in helping their child cope in the learning environment.

All students who have been diagnosed with ADD/ADHD require a full eye examination. The correction of refractive error can improve concentration and decrease distractive tendencies. In addition, Ritalin has been shown to exacerbate glaucoma in children. The optometrist must therefore examine all children for glaucoma before Ritalin is prescribed. The presence of glaucoma may negate the use of Ritalin, but in cases in which children with glaucoma are prescribed the medication, then eye exams should be performed three times yearly.

ALCOHOL ABUSE

Characteristics

Alcoholism is the state produced by ingestion of alcohol and is characterized by lack of coordination, belligerence, spouse abuse, hazardous behavior, and mood changes.

Epidemiology

Approximately 5% to 10% of the U.S. population is considered alcoholics. The cost of alcohol-related problems in the U.S. is nearly a third of a trillion dollars per year, mostly because of accidents, health problems, lost work, and crime. Car accidents related to alcohol consumption cause an average of 22,000 deaths per year and two million injuries. Each year, 5 million vehicles are damaged in such accidents.

Alcoholics reduce their lifespan by an average of 15 years.

Pathophysiology

Alcohol acts as a CNS depressant. It is rapidly absorbed, but is lethal in small amounts if tolerance has not been reached. Commonly ingested doses can cause tissue damage, particularly to the liver. For example, three to four drinks within a 24-hour period

will produce measurable liver damage. Alcohol should never be consumed at all during pregnancy as it may, even in small doses, produce fetal damage or death.

Precipitating Factors

A strong genetic proclivity exists towards developing alcoholism or dependency. The condition tends to run in families. The highest at-risk patient is the young adult who tolerates alcohol well and therefore feels that no risk is related to excessive drinking.

Diagnosis

Alcoholics tend not to fulfill major obligations at work and at home. They typically arrive late to work because of withdrawal symptoms ("hangover") in the morning. As the alcoholism worsens interpersonal relationship problems usually increase. The tendency to become disinhibited usually increases, leading to drinking and driving. Of all automobile accidents, half are attributable to alcohol consumption.

Tolerance is easily reached, and so increasing amounts of alcohol are needed to produce the desired effect. Drinking becomes "heavier," meaning a greater consumption for a longer period of time.

The related signs of alcohol abuse include chronic fatigue, poor nutrition, increasing frequency of household accidents, insomnia, neuropathy, seizures, and suicide attempts.

Diagnosis of alcohol abuse typically uses the CAGE questionnaire. The questionnaire asks the following four questions:

1. Have you ever felt the need to Cut down on your intake of alcohol?
2. Have you felt Annoyed by people criticizing your drinking?
3. Have you felt Guilty about your drinking?
4. Do you need an Eye-opener (or morning drink) to calm your nerves or treat a hangover?

If two questions are answered in the affirmative, then a 50% chance of alcoholism exists in this patient.

Treatment

The patient must commit to a lifetime of sobriety. The patient's entire life must be reoriented toward healthy living and appropriate choices. The patient must be made aware of the triggers that stimulate the desire to drink, and techniques must be taught on how to avoid these cues. Organizations such as Alcoholics Anonymous (AA) are committed to teaching the patient the appropriate techniques to manage a lifetime without alcohol.

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CHAPTER 20

In-Office Medical Emergencies

CHAPTER OUTLINE

A medical emergency that occurs in the eye doctor's office is typically unexpected, and is a frightening experience for the entire office staff. The chance of a successful outcome is increased when these emergencies are dealt with in a calm and appropriate manner.

The examiner should make every effort to prevent a medical emergency. The history is invaluable in helping the examiner to note those factors that predispose a patient to a possible medical emergency. These factors include a previous history of heart attack, stroke, congestive heart failure, asthma, chronic obstructive pulmonary disease (COPD), seizures, diabetes, and some medications.

Patients show significant and early signs and symptoms that herald a life-threatening medical emergency. Changes in the rate and quality of breathing may occur first. The skin may change color and become pale, flushed (red), or blue (indicating cyanosis). Abnormal sweating is often observed in medical crisis, and the patient may become panicked and begin to hyperventilate. The patient may become claustrophobic in the examination chair and have a strong desire, even to the point of aggression, to get up and leave quickly. The patient may exhibit an abnormal unsteadiness while standing, or a staggering gait. The patient may complain of chest pain, nausea, dizziness, or vertigo. These are all signs that an emergency crisis is imminent.

Management of in-office emergencies begins by becoming prepared for the most common emergencies. All members of the office staff, including support staff and doctors, should be trained in cardiopulmonary resuscitation (CPR). An office manual should be available that clearly delineates the office protocol to be followed in cases of syncope, diabetic shock, seizure, insect sting, stroke, and heart attack. These procedures must be committed to memory so that time is not wasted in looking up the protocol during the actual emergency. These procedures may be reviewed by staff members a few times per year during office meetings. Various medical supply companies sell professionally produced DVDs, CD-ROMs, and videos that present the appropriate procedures to follow during a medical emergency.

Remember, to prepare for an emergency in advance, the doctor should get training in CPR, prepare an emergency office manual and review it with the entire office staff, and view CD-ROMs, DVDs, and videos that pertain to in-office medical emergencies. The most common emergencies to prepare for include syncope, hyperventilation, seizures, diabetic shock, insect stings, myocardial infarction, and stroke.

SYNCOPE

Case 1

A 24-year-old medical student was seen in our eye clinic for a routine eye examination. During applanation tonometry she slumped out of the slit-lamp without warning, and fell to the floor unconscious. After 30 seconds she regained consciousness and was found to have low blood pressure (70/40) and the history revealed that she had anorexia and had not eaten all day. She was of low body weight for her height, and admitted to having been anxious about her examination since having watched tonometry performed that morning at her medical school. We diagnosed vasovagal (vasodepressor) syncope.

Syncope, or fainting, is a sudden, temporary, and transient loss of consciousness. It may be the result of a reduction of blood flow or glucose to the brain, or it may be related to central nervous system dysfunction. It commonly occurs in the office because of the stress, pain, claustrophobia, and ocular manipulation that are imposed on the patient by the ocular examination. Fainting in the optometry office most often occurs as a result of contact lens application, tonometry, and gonioscopy. In this case, the precipitating factor is obvious and the syncope is rarely determined to be caused by an emotional stress that leads to a drop in blood pressure. Of greater concern is fainting that occurs with no obvious relationship to a precipitating factor. Therefore, to deal with an in-office syncopic event, the practitioner must be aware of the causes of syncope, how to evaluate the unconscious patient, and how to successfully manage the loss of consciousness.

The Causes of Syncope

Almost half of all fainting episodes are the result of benign causes, while a third are caused by seizures, and the remainder by drugs or cardiac or metabolic disorders. A common type of syncope in the office is the vasovagal, or vasodepressor response. This type of fainting is because of an emotional stress, such as being in a warm or crowded room, fatigue, hunger, alcohol ingestion or ocular manipulation. The stress causes either a slowing of the heart rate, a drop in blood pressure, or both.

Blood pressure may also drop when a patient stands up quickly from the examination chair. This drop is known as orthostatic, or postural, hypotension. Patients who are prone to orthostatic hypotension include tall individuals, diabetics, senior citizens, pregnant women, and those who have been reclined for long periods of time for binocular indirect ophthalmoscopy.

Emotional upset may also lead to hyperventilation. Rapid breathing leads to physiological changes that result in cerebral vasoconstriction.

More serious causes of syncope include cardiac arrhythmias (which cause decreased cardiac output), myocardial infarction, and hypoglycemic shock.

Managing the Syncopic Event

The appropriate intervention begins with recognizing the earliest signs of an impending faint (Box 20-1). The patient may say that they feel lightheaded, dizzy, sweaty, or anxious. The examiner may note skin pallor, hyperventilation, and a loss of patient cognitive responses. The syncopic attack then proceeds to the characteristic fall of the patient to a supine position. Prevention of injury to the patient during the fall is of utmost importance. The examiner should guard the head of the patient to keep it from hitting the examination chair or instruments as the patient falls from a standing position. Or, if the patient is in the examination chair, the examiner should lean the chair back. The patient's head should not be allowed to fall below the level of his or her knees.

Recent studies have shown that the optimal position for a syncopic patient in a chair is leaning back with their head just above the level of their knees as this optimizes cardiac efficiency. If no warning period occurs, the patient may fall unexpectedly and without help. This can result in severe head or bodily injury. The examiner should note whether injury occurred during the fall to inform the emergency medical team (EMT), the patient's doctor, or hospital. If neck injury occurred, the examiner should not attempt to move the patient, because this may result in permanent spinal cord injury.

Emergency Evaluation of the Syncopic Patient

Once in the recumbent position, the examiner should assess the status of the unconscious patient. First, the examiner should shout out a code word that alerts the

BOX 20-1
STEPS TO MANAGE SYNCOPE

- Recognize precipitating factors.
- Recognize aura that precedes syncope.
- Immediately support standing patient.
- Immediately lie seated patient backward.
- Prevent injury during fall.
- Note whether neck injury occurred during fall.
- Place patient in supine position.
- Tap patient and shout.
- If patient is unconscious, call EMS (unless syncope is benign).
- Open patient's airway.
- Check patient for breathing.
- Check patient for pulse.
- If no pulse or breathing is detected, begin CPR.
- Avoid smelling salts.
- If syncope is benign, reassure patient after arousal.
- Encourage medical evaluation.

office staff that an emergency is in progress. In many clinics, the words "code blue" followed by the room number is repeated by the examiner until a staff member arrives to assist in the emergency.

With the patient recumbent in the examination chair or supine on the floor, the examiner should then check responsiveness by tapping gently on the patient's shoulder and shouting into the victim's ear "Are you OK?" If neck injury is suspected the patient, should not be moved.

Activation of Emergency Medical Services System

The next dilemma facing the examiner is the decision to activate the local emergency medical services (EMS) system, usually by dialing 9-1-1. The EMS system should always be activated if respiration or cardiac activity stops, if a stroke, epilepsy, or heart attack is suspected to be the cause of syncope, or if any injury was sustained in the fall. If the syncope is obviously the result of a vasovagal event, and pulse and breathing have not stopped, then the EMS need not be activated unless the patient does not reach consciousness in a reasonable amount of time. Any syncope in a child or infant necessitates EMS activation.

Emergency Intervention of the Syncopic Patient

If neck injury is not suspected, the examiner should roll the patient onto his or her back and open the airway, using techniques learned in CPR class. The examiner should check for breathing and if none is found, then initiate CPR.

In the vast majority of syncope cases, respiration and pulse will be present. At this point restrictive clothing around the patient's (and doctor's!) neck may be loosened to prevent suffocation. The area around the patient should be cleared of any instruments or articles that may cause injury. Pulse and respiration should be monitored during unconsciousness. Any deviation from normal heart rate or breathing mandates EMS activation.

The use of smelling salts remains controversial, and in most cases should be avoided. Smelling salts may cause a quick head-jerk reaction in a synoptic patient with a neck injury and can cause further spinal damage. It is best to allow the patient to rise from their stupor slowly with a minimum of intervention. A comfort blanket can be put under the patient's head as long as no injury is suspected, and a blanket can be placed over the patient's body for warmth. To help prevent shock during unconsciousness, the patient's feet may be slightly elevated.

In a case in which the syncopic patient is breathing normally and no evidence of head or neck injury is present, the patient may be placed into what is known as the recovery position. In the recovery position, the victim rests on his or her side with one hand under the head. This position allows for easier breathing and prevents the tongue from closing the airway.

Regaining Consciousness

All spectators not involved with the recovery should stand far away from the patient. The examiner should repeat the patient's name until consciousness is regained. The patient should be allowed to remain recumbent until he or she wishes to rise. Support will be needed until standing is achieved. The patient should be asked to sit down slowly and drink some water to treat possible dehydration. The examiner should ask the patient whether he or she has ever fainted before, what medications he or she is taking, what systemic diseases he or she has, how he or she is feeling now, and whether any history of epilepsy exists. The examiner should then take the blood pressure and pulse of the postsyncopic patient. If all findings are normal and the patient recovers well, the examination can continue. Further anxiety may preclude further examination. The examiner should assess the patient's ability to drive, and call or arrange for transportation if necessary. The optometrist should alert the patient's physician about the syncope. The primary physician may want to rule out significant causes of fainting such as cardiac arrhythmias, diabetes, drug-induced syncope, epilepsy, and stroke.

SEIZURES

Case 2

A 20-year-old family member of a cataract patient felt ill while watching a video of cataract surgery in our clinic. She suddenly lost consciousness, became rigid, and exhibited jerking of her face and limbs. She gradually returned to consciousness and became combative for a few seconds. She returned to normal mental alertness within minutes. A neurology examination eventually ruled out epilepsy.

A seizure is the result of an abnormal discharge of nerves and usually is characterized by 30 seconds to several minutes of involuntary jerking of one or more body parts, possible loss of consciousness and incontinence. Recurrent seizures are known as epilepsy, but seizures may be the result of hypoglycemia, drugs, or space-occurring lesions. One in every 200 individuals has epilepsy. Seizures do not always lead to fainting, but when there is a loss of consciousness associated with seizure activity the same steps should be followed as with syncope (Box 20-2).

In some cases of seizures, the patient does not totally lose consciousness but does experience a prolonged period of involuntary body movement. The examiner must prevent harm by moving all objects

BOX 20-2
STEPS TO MANAGE SEIZURES

- Recognize aura that precedes seizure.
- Protect patient during fall.
- Clear area.
- Keep patient's airway open.
- Put a handkerchief between patient's teeth (if possible).
- Do not restrain patient.
- Place pillow under patient's head.
- Loosen patient's neck clothing.
- Call EMS.

away from the supine patient. The examiner should not restrain the arms or legs of the patient. During the seizure a firm but soft object, such as a handkerchief, should be placed between the patient's teeth to prevent tongue biting. Hard objects should not be placed in the mouth because this may cause tooth breakage. The examiner should not put his or her fingers into the patient's mouth, because this may result in injury. The patient should not be allowed to swallow any objects.

The examiner should loosen any clothing around the patient's neck, put a pillow under the patient's head, and guard against bodily injury. As a patient regains consciousness after a seizure, he or she may become combative. The examiner should reassure the patient and tell him or her to lie still until he or she becomes less aggressive. The examiner should tell the patient what happened, and ask whether he or she had ever had a seizure. Patients who exhibit a seizure in the office must not be allowed to drive. Arrangements should be made for immediate evaluation by their primary physician or emergency room. Hospitalization may be required for a first-time seizure to determine the cause of the seizure and prescribe treatment.

Any seizure that lasts longer than 5 minutes should prompt activation of the EMS system by calling the appropriate telephone number (in most cases 9-1-1).

STROKE

More than a half million strokes occur in the United States each year, and approximately one third result in death.

Recognition of an Impending Stroke

A stroke should be suspected if the patient experiences difficulty talking or walking, a weakness on one side of the body, or sudden confusion or headache. If the examiner notes a sudden facial droop, unequal pupils, slurred speech, or confusion of the patient, stroke should be suspected.

Management of an Impending Stroke

If any question exists of whether a patient is experiencing a stroke, then activate EMS (Box 20-3). The patient should be reclined in the chair or be placed supine on the floor. Breathing and pulse should be monitored, and restrictive clothing around the neck should be loosened. If necessary, initiate CPR. The EMT should be informed of the exact signs and symptoms of the possible stroke, because this information may help in the treatment.

BREATHING EMERGENCIES

Conscious patients who develop labored respiration are considered a medical emergency. If breathing ceases, irreversible brain damage can occur in as little as 4 minutes. Cardiac arrest will ensue in 5 to 10 minutes. If breathing stops, the patient must be ventilated and his or her blood oxygenated by the use of chest compressions.

The two most common and significant systemic conditions that affect respiration include hyperventilation and asthma. Either of these may precipitate a true medical emergency in the office.

Hyperventilation

Anxiety is the most common cause of increased rate or depth of respiration, or both. When the patient's respiration rate increases above 25 breaths per minute, the carbon dioxide level in the blood decreases. The patient may become lightheaded or dizzy.

The treatment for hyperventilation is to have the patient breath into a paper bag. By rebreathing expired air, an increase in carbon dioxide in the blood occurs that results in an automatic reflex to reduce the respiratory rate.

Asthma

Characterized by a narrowing of the airways, asthma is a response to an environmental stimulus. Asthma may be an allergic response, or it may occur as a result

BOX 20-3
STEPS TO MANAGE IN-OFFICE STROKES

- Recognize signs and symptoms of cerebrovascular accident (CVA).
- Place patient in a reclining or supine position.
- Activate EMS.
- Monitor patient's breathing and pulse.
- Initiate CPR if necessary.
- Relate patient's signs and symptoms to EMT.

of stress, anxiety, or cold, dry air. It is very common and occurs in as much as 5% of the U.S. population. The treatment of asthma is the use of a sympathomimetic or anticholinergic agent in the form of a bronchoinhaler. The examiner is encouraged to help locate the inhaler that the patient uses and to assist in administration of the drug. If relief does not occur quickly, then EMS should be activated.

MYOCARDIAL INFARCTION

Case 3

A 68-year-old male was slumped in his chair in our waiting room. No symptoms preceded the event. He was found to have lost consciousness and was unresponsive to auditory stimulus. No pulse or respiration was present. CPR was immediately performed. After transportation to the hospital, he was found to have suffered a myocardial infarction. His physician credited his survival to appropriate CPR technique and the quick emergency team response.

An increased risk of heart attack exists in patients older than 50 years who have a positive family history of heart disease, who are hypertensive, diabetic, sedentary, smokers, or who have elevated blood cholesterol. More than one million heart attacks occur in the United States each year, causing 600,000 deaths, among patients older than 65 years of age. A heart attack occurs when blood supply to the heart muscle is deficient, usually because of an occluded coronary artery. The patient experiencing a heart attack often exhibits an increase in heart rate and breathing, pallor, and coolness of the skin. Substernal pain radiating to the arms or back may or may not be present. The pain typically lasts 15 minutes to hours.

Chest pain because of heart disease is described as a dull, aching substernal discomfort that may radiate to the arms or jaw. In some cases the pain is heavy and squeezing, and is associated with nausea and vomiting. Hyperventilation and anxiety often accompany chest pain.

Chest pain may be the result of angina pectoris or myocardial infarction. Angina pectoris is defined as the onset of chest pain that is relieved by the administration of nitroglycerin. If the patient has a history of angina pectoris and experiences chest pain during the eye examination, then he or she should be allowed to ingest the dose of nitroglycerin. If the chest pain is not relieved in 15 minutes, then the pain should be considered a heart attack and EMS should be activated (Box 20-4). If the patient has not been diagnosed with angina pectoris and therefore has no nitroglycerin, then any symptom of chest pain warrants an immediate activation of the EMS system.

If a patient experiences the signs and symptoms of a myocardial infarction, EMS should be immediately activated. These symptoms include a crushing, substernal pain, a cold sweat, apprehension and anxiety, and hyperventilation. Oxygen should be administered if it is available. If respiration or the heart ceases, then CPR should be initiated. Portable defibrillations are now being placed on aircraft and in most shopping malls. These devices are becoming less expensive and may be efficacious in large eye clinics.

BOX 20-4
STEPS TO MANAGE HEART ATTACK

- Take CPR course.
- Recognize signs of MI.
- Place patient into reclining or supine position.
- Call EMS.
- Check patient responsiveness.
- Open patient's airway.
- Check patient's breathing.
- Check patient's pulse.
- If no pulse is detected, initiate CPR.

DIABETIC EMERGENCIES

Almost one tenth of the U.S. population has diabetes mellitus. The acute consequences of insulin insufficiency include hyperglycemia, diabetic ketoacidosis, blurred vision, neuropathy, and renal disease. Too little insulin can result in diabetic coma. Conversely, hypoglycemia can result from too much insulin and can lead to insulin shock. Both conditions are medical emergencies that need immediate intervention.

Recognizing the Diabetic Emergency

The hyperglycemic patient may present with complaints of increased thirst and respiration, usually hyperventilation. Cognitive functioning may be reduced; the patient is decidedly not hungry. The hyperglycemic patient frequently urinates, is tired, and has a headache. The vision may become blurred, and the skin flushed, hot, and dry. Eventually, the patient becomes disoriented and confused.

Hypoglycemia occurs if the patient has not eaten for several hours. Symptoms include an increase in hunger, cold and wet skin, and lethargy.

Treatment of the Diabetic Emergency

The emergency treatment for both impending hyperglycemic and hypoglycemic crisis is to activate EMS and give the patient sugar (Box 20-5). It is a good idea to keep orange juice in the office for such emergencies. The examiner should pour several tablespoons of sugar into the orange juice and have the patient drink as much as possible. It may be difficult

BOX 20-5
MANAGING DIABETIC EMERGENCIES

- Identify patient with diabetes
- Recognize symptoms of crisis
- Call EMS
- Have patient drink orange juice with added sugar
- If patient is alert, have him or her inject insulin
- Do not inject insulin yourself
- Transport patient to hospital

to differentiate hyperglycemia from hypoglycemia in a diabetic emergency, so when in doubt, give sugar. Sugar will not hurt the hyperglycemic. This patient, who is slipping into coma because of too little insulin, needs transportation to the hospital as quickly as possible. Insulin will be given in the hospital. If the patient is not coherent, he or she should not be given an insulin injection in the office. The wrong amount can cause harm.

Sugar will help the hypoglycemic avoid diabetic shock. This patient also should not be injected with insulin, but needs transportation to the hospital.

INSECT STINGS

The Hymenoptera order of insects includes bees, wasps, ants, hornets, and yellow jackets. The sting of one of these insects can produce a severe reaction in sensitive individuals. Prompt recognition of this reaction and appropriate management may prevent coma and death.

After a sting to a patient allergic to the insect, an itchy, local reaction may appear within seconds. Within minutes, bodywide itching can occur. At this point, the patient may exhibit an acute anxiety reaction, sometimes accompanied by hyperventilation. The patient can become nauseous and experience abdominal upset. Bronchospasm may ensue and lead to respiratory distress. In just 15 to 20 minutes, vasodilatation can lead to hypotension, shock, and death.

The immediate treatment of bee-stings begins with removal of the stinger if it is still present in the wound. A needle-tip or forceps can be used to remove the stinger. The venom sac should not be squeezed, because this may inject additional venom into the area of the sting.

After stinger removal, the area should be cleaned with cool water and soap. The local reaction should be treated by elevating the area and applying cold compresses. A patient with known insect-sting hypersensitivity, or who begins to experience respiratory distress, must be rushed to the nearest emergency room as quickly as possible. EMS should be activated if no immediate transportation is available.

Emergency Treatment of the Stung Patient

The hypersensitive patient requires injection of epinephrine to reduce body-wide itching (urticaria) and relieve bronchospasm (Box 20-6). In addition, an antihistamine (i.e., diphenhydramine [Benadryl]) can be injected and swallowed to reduce the systemic reaction. Oxygen should be administered to all patients in respiratory distress.

The Insect-Sting Kit

Commercial anaphylaxis kits may be obtained by prescription and stored in the optometric office for use in bee-sting emergencies. Kits such as Ana-Kit and EpiPen include syringes preloaded with epinephrine, antihistamine tablets, and a tourniquet. The tourniquet is placed proximal to the site of the sting if it is on an extremity, to reduce distribution of the toxin. The patient can self-inoculate, or the optometrist may inject the epinephrine. The patient then swallows the antihistamine tablets and is taken immediately to the nearest emergency room.

CONCLUSION

Prompt recognition and intervention of a medical emergency is the surest way to prevent a catastrophe. The optometrist should prepare in advance for syncope, hyperventilation, seizures, heart attack, diabetic crisis, and insect stings by having the entire office staff take a CPR course, view training tapes, DVDs, and CD-ROMs on emergency intervention, develop an office manual on emergency protocols and commit it to memory, run mock emergency drills in the office, and stock emergency medications such as injectable epinephrine, oral antihistamines, oxygen, and sublingual nitroglycerin tablets in the office. The single most significant factor in emergency intervention is the activation of the EMS system.

BOX 20-6
MANAGING INSECT STING (HYPERSENSITIVE PATIENT)

- Have Ana-Kit in office.
- Without squeezing, pull out stinger.
- Rinse area with soap and water.
- Use tourniquet if extremity is involved.
- Watch patient for respiratory distress.
- Call EMS if patient's breathing is labored.
- Inject epinephrine.
- Have patient swallow antihistamine.
- Transport patient to emergency room.

EMERGENCY INTERVENTION AND THE LAW

Good Samaritan laws exist to protect the rescuer in the event that the patient is hurt or dies during emergency intervention. These laws extend, at least partially, to the optometric private practice. As long as the optometrist intervenes in a medical emergency in an appropriate manner, and is deemed to have followed a protocol that any reasonable optometrist would follow in the event of a medical emergency in the optometric office, then the optometrist would most likely not be found to be negligent, even if injury to the patient results from the intervention.

If, however, the optometrist is found to have caused injury or death because of the inappropriate application of emergency procedures, or the failure to have adequate knowledge to appropriately intervene in a medical emergency, the optometrist may be found culpable on the basis of negligence, and good Samaritan laws may not apply in this case to trained professionals.

What, then, does a reasonable optometrist need to know to meet the standard of care in emergency situations as it applies to optometry? First, it would be expected that all optometrists be certified in CPR, and take recertification to prevent expiration. It may also be expected that at least some office personnel be trained in CPR.

Second, an office manual with emergency protocols may demonstrate to a jury that you are aware of the potential medical emergencies that can occur in your office and that you and your staff prepared in advance for a crisis.

Third, a reasonable optometrist should have a blood pressure cuff and stethoscope. In addition, orange juice and sugar for diabetic emergencies may be essential in the office.

You should contact your state board of optometry to ask if your state therapeutic bill requires emergency medication or devices in your office. If your bill allows for indictable, then you should keep an insect sting kit in your office.

The optometrist would not likely be expected to have sublingual nitroglycerin tablets, oxygen canisters, injectable antihistamines, or a defibrillator in the office. Therefore, failure to possess these items would not constitute negligence in a medical emergency.

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CHAPTER 21

Anterior Uveitis and Systemic Disease

CHAPTER OUTLINE

Inflammation of the anterior uveal tissues may be caused by the presence of systemic disease. Anterior uveitis is often the first symptom of a serious underlying disorder. Therefore, the management strategy often involves topical therapy in addition to laboratory testing and multidisciplinary involvement to identify an associated systemic etiology.

In at least 1 of 6 cases of anterior uveitis, an associated systemic disease can be ultimately identified. In approximately 3 of 4 cases of anterior uveitis, however, an etiology of any type is never found. Consequently, the disease can be frustrating to both doctor and patient.

In general, anterior uveitis is fairly straightforward to diagnose. The presence of white blood cells in the anterior chamber of the eye is pathognomonic of the disease. The treatment is typically effective and simple, and in most cases anterior uveitis resolves with no significant sequelae.

Although typified by an uneventful resolution, anterior uveitis may cause severe and permanent ocular complications. For example, the presence of keratic precipitates on the corneal endothelium may reduce the effectiveness of the corneal endothelial pump and disrupt normal corneal physiology, thus leading to stromal clouding. In addition, anterior and posterior synechiae can lead to uveitis-related glaucoma, and chronic anterior uveitis increases the risk of cataract formation.

Anterior uveitis becomes particularly challenging in recurrent, bilateral, chronic, or recalcitrant cases, in addition to those that involve the posterior segment. These characteristics, in addition to cases unresponsive to treatment, often indicate the presence of an underlying disorder. The management of such complicated cases becomes compounded by the need for laboratory investigation and medical specialty involvement.

The diagnosis and treatment of anterior uveitis without considering the possibility of an underlying systemic disease is considered inadequate medical interdiction. Minimally, an extensive uveitis history on every patient who presents with anterior uveitis can help screen for a potential systemic disorder. Any indication of an associated disease, whether by history, uveitic characteristics, or concurrent systemic signs or symptoms, warrants a laboratory evaluation.

CLASSIFICATION OF ANTERIOR UVEITIS

Anterior uveitis is a broad definition used to denote inflammation of the tissue components of the anterior uveal tract. Inflammation confined to the anterior chamber indicates involvement of the iris and is consequently known as iritis. If only the ciliary body is inflamed, then the disorder is termed cyclitis. Iridocyclitis is defined as inflammation to both the iris and ciliary body. The more posterior the inflammation, the greater the likelihood that it is caused by a systemic disease and the more difficult it will be to treat.

Acute uveitis is typically intraocular inflammation that lasts no longer than 6 weeks, while chronic cases persist longer. In general, the more posterior the inflammation, the longer it will last. Chronic uveitis increases the likelihood of an associated systemic disease, and short-lived acute cases are more likely to be caused by local or environmental factors.

Anterior uveitis may be unilateral or bilateral in presentation. Bilateral uveitis has a greater association with systemic disease than the unilateral presentation.

A uveitis that is seen more than once is known as recurrent uveitis. Recurrent uveitis has a greater risk of associated systemic disease. A patient with a first-time occurrence of anterior uveitis is considered at low risk for systemic disease, unless other factors are present such as concurrent systemic symptoms, bilaterality, posterior segment involvement, intraocular complications, and resistance to treatment.

If the etiology of the uveitis is never discovered, then the inflammation is termed idiopathic. Idiopathic inflammation is the most common form of anterior uveitis, because in most cases the cause of the disease is never discovered.

If a cause is isolated, however, then the uveitis may be noninfectious or infectious. Causes of noninfectious anterior uveitis include systemic disease-associated uveitis and trauma. Infectious uveitis may be the result of bacterial, viral, fungal, or parasitic infection.

Uveitis may be associated with a granulomatous condition. In granulomatous uveitis a deposition of large, fatty-appearing congregations of white blood cells known as "mutton-fat" keratic precipitates is present, primarily on the corneal endothelium. These precipitates may also occur on the iris, lens, vitreous, and retina. The presence of granulomatous uveitis increases the likelihood of an associated granulomatous systemic disease. Nongranulomatous uveitis fails to reveal any evidence of a granulomatous nature and the keratic precipitates will be small and discrete. Nongranulomatous uveitis has a reduced risk of associated systemic disease.

The term "posterior uveitis" indicates inflammation of the posterior uveal tract. More specifically, choroiditis is used to describe an inflammation of the choroid. Posterior uveitis is rarely confined to just the choroidal tissue, however, because of the intimacy of the retina. If the pars plana becomes inflamed it is termed "pars planitis," or intermediate uveitis. Inflammation of the overlying retina, or retinitis, is typical in many cases of choroiditis. Active cases of retinitis often produce inflammation of the overlying vitreous, or vitritis.

In extreme cases of uveitis, all the internal tissues of the eye may become involved. This is known as endophthalmitis. Panophthalmitis describes the inflammation of both internal and external tissues of the eye.

On the basis of these definitions, the relative risk of a systemic disease associated with a uveitis can be predicted to some degree. The least risk for a systemic disease occurs in a patient with a first occurrence of unilateral, noninfectious, acute nongranulomatous iritis. The greatest risk for a systemic disease occurs in a patient with recurrent, bilateral chronic granulomatous anterior uveitis with posterior involvement.

PATHOPHYSIOLOGY OF ANTERIOR UVEITIS

Inflammation of the iris is not visualized well because the tissue swells along the anteroposterior axis of the eye. As such, a thickened iris could only be detected in cross-section by use of ultrasound biomicroscopy. Visual assessment of the inflamed iris in the slit lamp reveals no indication of its edematous condition except for possible narrowing of the anterior chamber angle. Likewise, swelling of the ciliary body is practically undetectable, and may only cause some accommodative changes in the uveitis patient. The swelling of these tissues is detected by their release of white blood cells into the aqueous. Cells detected in the anterior chamber indicate an iritis, and cells visualized in the potential space between the iris and the vitreous are produced by an inflamed ciliary body.

Inflammation of the iris promotes migration of white blood cells and protein into the anterior chamber by causing a breakdown of the blood-aqueous barrier. These extravasated cells help mediate the inflammatory response, and are a crucial element in the immune response of the eye. In the absence of anterior uveitis, the anterior chamber should be free of cells.

The cells that migrate into the aqueous from the iris or ciliary body are primarily lymphocytes, though there may be a significant number of neutrophils present in the aqueous. Other white blood cell types can also be identified in almost all cases of uveitis.

The diverse cell types found in the aqueous of uveitis patients indicates that elements of all four hypersensitivity reactions are present in almost all cases of anterior uveitis. Type I hypersensitivity reactions, mediated by antibodies such as immunoglobulin E (IgE), binds mast cells to basophils, causing their breakdown and release of histamine. An example of a Type I reaction is hay fever, but the role of mast cells and basophils in anterior uveitis is still unclear.

Type II reactions are mediated by cytotoxic antibodies and cause hemolytic disorders (such as blood transfusion reactions), and are of little impact in the typical case of anterior uveitis.

Type III reactions are known as immune complex-mediated inflammatory response. In these cases, antibodies bind to antigens, causing deposition of these complexes with activation of the complement cascade and ultimate attraction of tissue-destroying cells. This type of reaction is a limited contributor to the inflammation produced in anterior uveitis.

The Type IV hypersensitivity reaction is mediated solely by T cells and is termed a cell-mediated immune response. The response seen in anterior uveitis is predominantly a T-cell-mediated mechanism.

The aqueous of the inflamed eye may demonstrate not only white blood cells, but also the presence of red blood cells, indicating hyphema, and pigment cells. The presence of even a trace amount of leukocytes in the anterior chamber is the strongest indicator of anterior uveitis. Erythrocytes in the anterior chamber indicate possible trauma or a severe acute iritis. The most common causes of pigment cells in the anterior chamber are the pharmacological introduction of topical phenylephrine (for pupil dilation), trauma, pigment dispersion syndrome, pigmentary glaucoma, and anterior uveitis.

Protein in the anterior chamber appears as flare, or a fog, visualized in the slit-beam of the biomicroscope. In the absence of anterior uveitis, only a slight amount of flare at most should be detected under the brightest illumination. Flare is a significant indicator of a breakdown in the blood-aqueous barrier. This sign is typical in cases of acute, severe iritis, but may be present chronically after ocular surgery or several bouts of anterior uveitis. Flare, in the absence of cells, does not require treatment, because it is not an indicator of active uveitis. The most common cause of flare is traumatic uveitis, because the concussive shock wave causes immediate and dramatic dilation of iris and ciliary body blood vessel. Traumatic effects on the intraocular tissues allow protein ample opportunity to escape the blood-aqueous barrier and leak into the anterior chamber.

Resolution of the anterior uveitis, either with or without treatment, occurs as the cellular components of the inflammation are reabsorbed into the trabecular meshwork. During time, an eventual clearing of the cells and protein occurs. The longer these immune components exist in the anterior chamber, the greater the chance of complications arising from their presence. Therefore, it is imperative to institute treatment as quickly as possible to expedite the clearing of these immune products from the aqueous.

SYMPTOMS OF ANTERIOR UVEITIS

The issue of photophobia is significant in the diagnosis of anterior uveitis. The most common complaint of patients with acute iritis is an aversion to bright light. Although some patients would describe photophobia as painful, more often it is an irritation that arises when exposed to brilliant illumination. The patient who arises in the morning with an iritis that developed during the night usually complains of photophobia when opening the shades of his or her bedroom and looking at sunlight, but photophobia is much less frequent in cases of chronic uveitis. Because chronic anterior uveitis is more often associated with systemic disease, the complaint of photophobia will decrease, but not eliminate, the possibility of an associated systemic disorder.

Vision is rarely affected by anterior uveitis. In most cases, only a mild subjective complaint of some visual blur will be present. Several factors can cause the subjective complaint of blurred vision. In anterior uveitis, lid, tear film, corneal, anterior chamber, iris, lenticular, and posterior tissue involvement may be present.

Ptosis can occur in anterior uveitis when the patient forcibly holds shut the upper lid of the involved eye until seeking help. This mechanical ptosis is transient, and not directly related to the uveitis, but still can cause blurry vision when the patient attempts to use the eye.

Profuse tearing is not uncommon in cases of acute uveitis, and increases with photophobia. Chronic and low-grade uveitis has much less associated tearing. A large tear lake is often responsible for the complaint of visual blur.

If a significant amount of immune product is deposited on the corneal endothelium, a degradation of the corneal endothelial pump may be present. A reduction in the effectiveness of this pump can lead to corneal swelling and cloudiness that patients describe as a visual blur or halos around lights. The patient may describe the vision as “foggy,” or like “looking through a cloud.”

An elevation in intraocular pressure can also cause a reduction in the effectiveness of the corneal endothelial

pump. Uveitis-associated glaucoma can lead to visual blur because of corneal swelling. The glaucoma may be the result of a closed angle from a swollen iris, or a pupillary block secondary to posterior synechiae. In the case of pupillary block, a subsequent iris bombe forces the iris forward and closes the angle. In most cases of anterior uveitis, a reduction of intraocular pressure is present that is mostly the result of an increase in the uveoscleral outflow mechanism and a slight reduction in aqueous production. In this manner, an elevation in intraocular pressure that would be expected because the trabecular meshwork is clogged with cellular debris is offset by an increase in uveoscleral outflow and reduced aqueous production.

Extensive corneal endothelial deposits may themselves reduce vision by obscuring the visual axis.

Several factors, if present in the anterior chamber of the inflamed eye, may cause visual blurring. Cells and flare, if profuse and centrally located, can cause complaints of hazy vision. Hypopyon, a thick cellular and dramatic response, can cover the visual axis and obscure vision. In some extreme cases of recalcitrant uveitis that resists treatment, the hypopyon may be cultured using fine-needle paracentesis to identify a possible pathogen (Figure 21-1).

Hyphema, a deposition of blood in the anterior chamber, may also be so thick and profuse that it too covers the visual axis, thus obscuring the vision of the patient (Figure 21-2).

Posterior synechiae, the abnormal attachment of the iris to the anterior lens capsule, can obscure the visual axis and cause blurred vision. This condition is rare, however, because most posterior synechiae form along the pupillary border and away from the visual axis.

Anterior uveitis can contribute to the formation of cataracts. Chronic or recurrent uveitis can be so disruptive to normal intraocular physiology that the clarity of the lens cannot be preserved. In addition, topical steroids used to treat anterior uveitis can cause the formation of posterior subcapsular cataract.

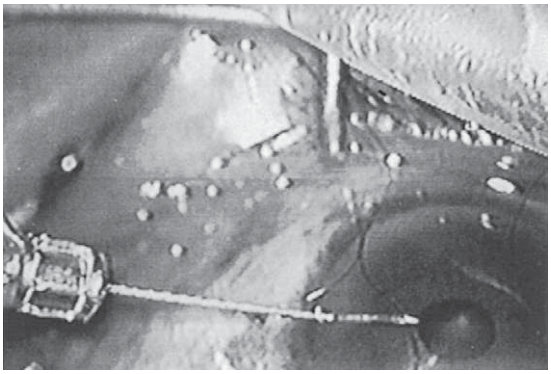

FIGURE 21-1 ■ Fine-needle aspiration (paracentesis) of a hypopyon for culturing and pathologic evaluation.

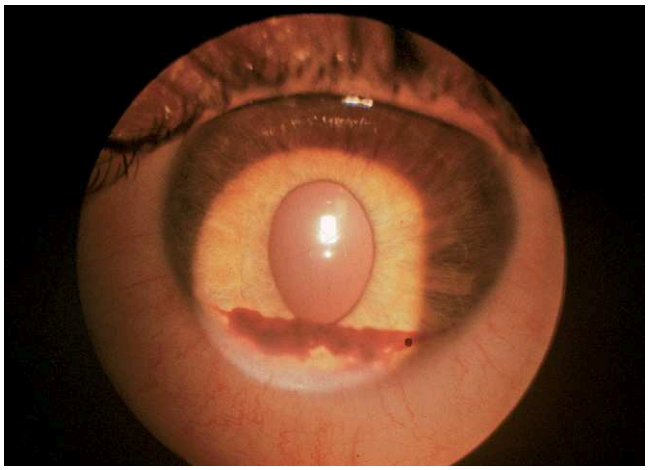

FIGURE 21-2 ■ Resolving hyphema in a case of juvenile xanthogranuloma. Note dark area of blood in the anterior chamber transversing the view of the inferior pupil and iris.

More posterior causes of visual blur include vitritis, retinitis, choroiditis, vasculitis, macular edema, and disc edema. Any case of anterior uveitis warrants a dilated posterior evaluation to monitor for any of these conditions. A uveitis that involves posterior structures will be more difficult to treat, has a greater risk of complications, and has a greater frequency of systemic disease association. In addition to visual blur, the most common symptom of a posterior involvement of the uveitis is the presence of floaters. These floaters are usually cellular debris and immune products that form in the vitreous and are seen by the patient, often against a blue sky or a white wall.

Finally, the patient with anterior uveitis may complain of a red eye. Acute uveitis has greatest risk of red eye, and chronic anterior uveitis may be seen with a white and uninvolved conjunctiva. Therefore, the patient with uveitis who is seen with a white eye is at greater risk of an associated systemic disease than the patient with red-eyed uveitis.

In summary, systemic disease should be suspected in cases of chronic anterior uveitis when the patient with a nearly white conjunctiva who has minimal photophobia complains of significant blurring of vision and floaters. Acute anterior uveitis with severe photophobia and redness, but hardly any visual blur or floaters, is less likely to be associated with a systemic disease.

HISTORY

The uveitic patient will often wait no longer than 2 days after the onset of symptoms to seek help. On the first day, the involved eye typically becomes red and photophobic. On the second day, the condition worsens to the point that the patient cannot work because

of extreme light sensitivity and ocular irritation or pain. Any patient who calls with complaints of a red, photophobic eye, should be seen immediately to confirm the presence of anterior uveitis.

The examination of the patient with a red, photophobic eye should be directed toward the detection and confirmation of an anterior uveitis. To this end, the history should narrow quickly to specifics about the ocular inflammation. After anterior uveitis is confirmed, a uveitis history is taken with regard to systemic disease.

The general history should include all patient demographics, because these can have an impact later on the search for a systemic disease. It is important to note whether this episode of inflammation has occurred in the past, whether it was ever evaluated or treated, and whether any systemic diseases were suspected. The names and addresses of previous treating practitioners should be noted so that previous episodes can be confirmed, thus helping establish the diagnosis of recurrent uveitis.

It is important to establish how the inflammation was first detected by the patient, what its course has been, and whether the patient is self-medicating. Any symptomology, such as pain, tearing, or photophobia, should be established. It is significant to note any concurrent body wide symptoms, because these may help in the detection of systemic disease. Such symptoms include hot or cold spells, malaise, rashes, cough, headache, or neck ache. It is appropriate to wait until the uveitis is established before asking these medical questions as part of a comprehensive uveitic history.

DIAGNOSIS

Visual Acuity

Most patients will be evaluated with the Snellen chart, which is adequate for patients with good visual acuity (VA). In patients with subnormal vision, low vision charts are a good option. For bedside patients, the "C-PAC" pocket low vision chart created by Dr. Connie Chronister is a portable and reliable method of establishing visual acuities in low-vision patients with uveitis. In acute, anterior uveitis, the VA is typically unaffected or reduced by only a line or two. The greater the reduction in visual acuity, the greater the risk of posterior involvement.

External Examination

The skin of the lids should be evaluated closely in patients with uveitis. Any growths or tumors of the lids should be measured and a referral to dermatology be considered for eventual biopsy. Granulomas of the skin or lid may occur in association with anterior uveitis and indicate an underlying granulomatous condition (Figure 21-3). The presence of any lid lesions in association with an anterior uveitis increases the likelihood of a systemic disease.

Extraocular Muscles

It is unusual to find extraocular muscle involvement in cases of anterior uveitis. If a finding of tropia or internuclear ophthalmoplegia in association with a uveitis is present, a common causal etiology may exist within the central nervous system. Multiple sclerosis, sarcoidosis or non–Hodgkin's lymphoma should be suspected in any patient who has anterior uveitis with diplopia, tropia, or extraocular muscle palsy.

Pupils

Anterior uveitis typically produces a miotic pupil on the involved side. Therefore, anisocoria is usually present in cases of acute unilateral anterior uveitis. The miosis is not the result of a neurologic lesion but is an effect of chemical inflammatory mediators on the receptor sites of the pupillary sphincter.

Unlike acute uveitis, recurrent uveitis may yield iris atrophy, mydriasis, and reduce the speed of pupillary constriction. Fuch's heterochromic iridocyclitis, for example, causes iris atrophy and pupil dilation when compared with the uninvolved side (Figures 21-4 and 21-5). Often the speed of pupil constriction on the involved side is reduced and almost extinguished.

In general, pupillary miosis is more common in acute iritis than in chronic anterior uveitis. Therefore, miosis is not an indication of an associated systemic disease.

Posterior synechiae may reduce pupillary functioning, cause a permanent distortion of the pupil, and eventually become cosmetically unappealing.

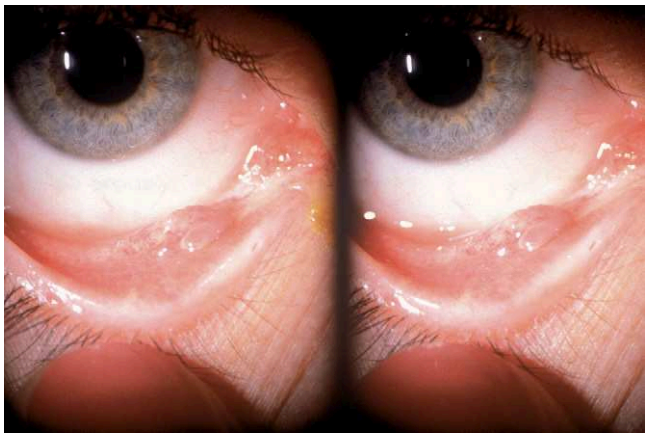

FIGURE 21-3 ■ Sarcoidosis with lid granulomas. Biopsy of these lid lesions can confirm the presence of sarcoid.

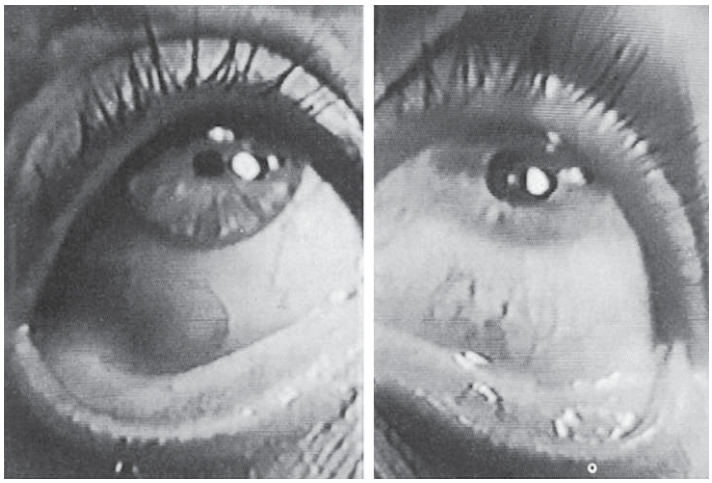

FIGURE 21-4 ■ **A,** Normal right eye reveals small pupil, good iris detail, and dark blue color. **B,** Involved left eye reveals the classic characteristics of Fuch's heterochromic iridocyclitis: a mid-dilated pupil, loss of iris detail, and a pale blue color.

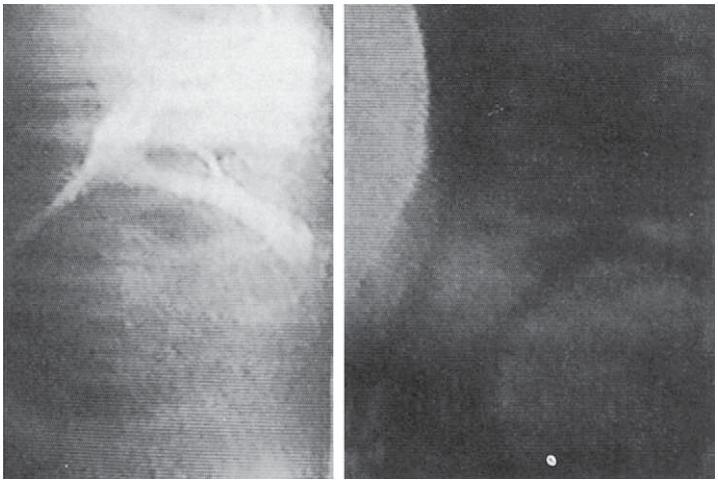

FIGURE 21-5 ■ **A,** Atrophy of the iris stroma reveals a "moth-eaten" appearance. **B,** The same area of iris reveals transillumination of the area of atrophy.

Intraocular Pressure

Intraocular pressure (IOP) is best measured using applanation tonometry with anesthetic but without fluorescein, because fluorescein can enter the anterior chamber and obscure the amount of cell and flare that is present. In addition, fluorescein may obscure posterior segment evaluation for as long as 24 hours and prevent the use of fluorescein angiography if it is necessary.

The IOP typically elevates in the first hours of an anterior uveitis, because aqueous cells get swept into the angle and physically clog the trabecular meshwork. This effect is short-lived and rarely observed in the office, because most patients are not seen within hours of the onset of anterior uveitis. Rather, the patient with uveitis is usually seen a day or 2 after its onset, by which time the IOP has decreased below normal. This drop in IOP is the result of the inflammatory effect on the uveoscleral outflow mechanism. In addition, uveitis has a slight effect on reducing aqueous production from the ciliary body. Therefore, most uveitis patients exhibit a reduced IOP on the side of the uveitis. This accounts for the time honored, and not particularly accurate phrase, "A sick eye is a soft eye."

An elevated IOP in cases of anterior uveitis may be caused by glaucomatocyclitic crisis (or Possner-Schlossman syndrome), or uveitic glaucoma. Intraocular tumors may contribute to an elevated IOP in association with cells in the anterior chamber. A diligent search for an intraocular tumor should be initiated whenever there is unilateral elevation of the IOP in association with cells in the anterior chamber.

Slit-Lamp Biomicroscopy

Conjunctiva

The classic conjunctival injection pattern of the acute anterior uveitis is a red circumcorneal flush. This limbal injection is often noted to be almost 360 degrees around the cornea. It represents a reflection on the conjunctival surface of deeper iris or ciliary body inflammation.

This limbal injection is to be differentiated from the injection patterns of conjunctivitis (Figure 21-6). In bacterial conjunctivitis, a deep red injection pattern is typically present that is greatest in the fornices and lessens towards the limbus. In viral conjunctivitis a superficial pink injection is usually present that is uniform over the entire bulbar conjunctiva, and in allergic conjunctivitis a classic swelling of the conjunctiva occurs so that the cornea appears to be sunk into it in a classic "watchglass" appearance.

The circumlimbal flush is typical in acute iritis but nearly or completely absent in chronic anterior uveitis. Therefore, the absence of circumcorneal injection in a case of anterior uveitis increases the likelihood of a systemic disease as a cause of the ocular inflammation.

Cornea

Convection currents are established in the anterior chamber by the aqueous rising up near the warm iris and then falling near the relatively cooler cornea. White blood cells circulate along these aqueous currents, being driven into the superior anterior chamber and then falling along the corneal endothelium toward the inferior angle. When the white blood cells hit the corneal endothelium they may get caught in irregularities such as guttata. The deposited cells send out chemical messengers to attract other white blood cells to the site. Accumulations of these white blood cells are known as keratic precipitates (KPs) (Figure 21-7). They typically form in the inferior cornea and frequently take on the shape of an inverted triangle (Arlt's triangle).

Neutrophils, macrophages, and lymphocytes are typically found within the KP. Large deposits are known as "mutton-fat" KPs and are typical of granulomatous disease (Figure 21-8). Small KPs are usually nongranulomatous and less likely to be associated with systemic disease.

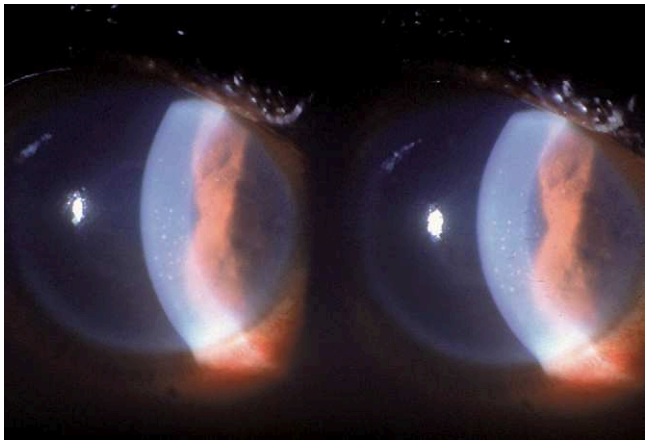

FIGURE 21-7 ■ Keratic precipitates on the corneal endothelium. These small KPs are usually the result of nongranulomatous disease.

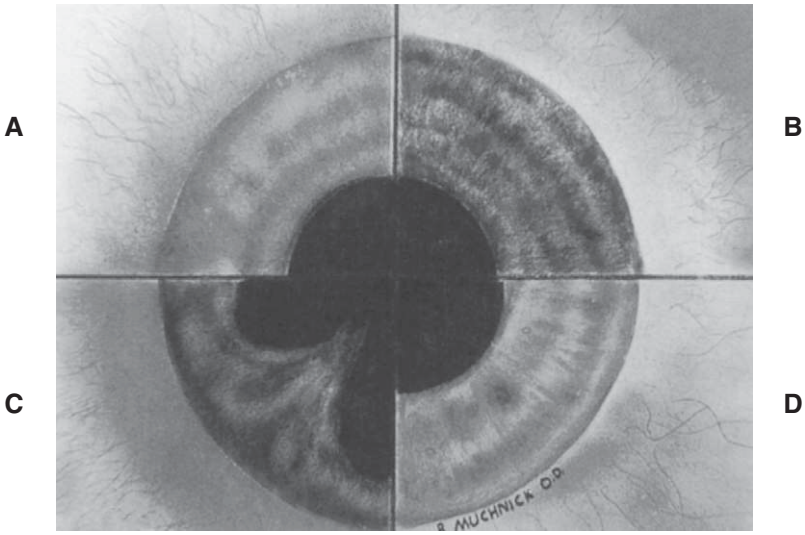

FIGURE 21-6 ■ Conjunctival injection patterns in conjunctivitis and uveitis. **A,** Acute uveitis demonstrates circumcorneal flush. **B,** Bacterial conjunctivitis demonstrates greatest injection in the fornices. **C,** Allergic and viral conjunctivitis demonstrates an overall pink injection pattern. **D,** Chronic uveitis demonstrates either a white and quiet conjunctiva (as in juvenile rheumatoid arthritis) or a moderate circumcorneal injection pattern seen here.

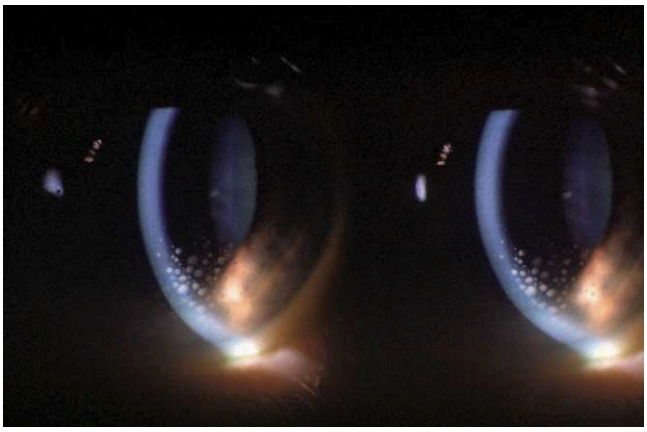

FIGURE 21-8 ■ "Mutton-fat" keratic precipitates. These larger KPs are likely the result of granulomatous disease processes.

After resolution of the uveitis, KPs may take from weeks to years to clear from the cornea. The risk of an associated systemic disease increases as the size and number of KPs increases. Granulomatous KPs indicate the presence of a granulomatous systemic disease.

Anterior Chamber

Neutrophils and lymphocytes spill over from the inflamed iris or ciliary body into the aqueous and can be observed on slit-lamp exam. The presence of these cells is pathognomonic of anterior uveitis (Figure 21-9). The anatomical classification of anterior uveitis can be determined by the position of the cells. White blood cells confined to the anterior chamber indicate the presence of an iritis, and if the anterior chamber is clear but cells are present just behind the lens and in front of the vitreous, then a cyclitis is present. Iridocyclitis causes cells to migrate to both positions. The further posterior the position of the cells, the greater the likelihood of systemic disease, the greater the risk of complications, and the more difficult it will be to treat the uveitis.

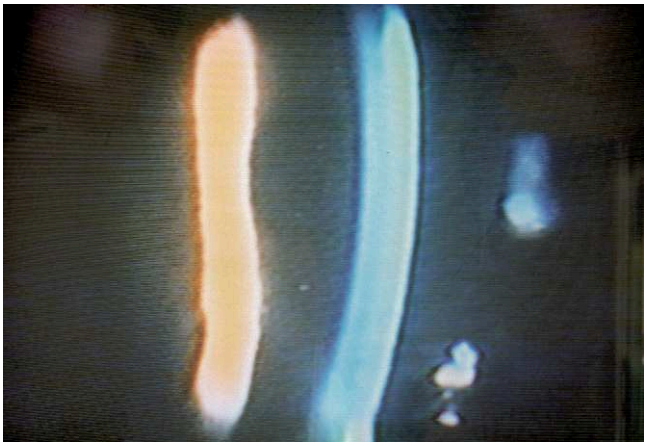

FIGURE 21-9 ■ Cells in the anterior chamber. Grade 2 cells represent a moderate uveitic reaction.

A profuse cellular response (Figure 21-10) may congeal with fibrin to produce a hypopyon that collects in the inferior angle of the eye (Figure 21-11). The presence of a hypopyon also increases the risk of an associated systemic disease, particularly Behçet's disease.

Flare, a proteinaceous exudate from the inflamed iris or ciliary body, is typical of acute and traumatic iritis, and is thus not indicative of an associated systemic disease (Figure 21-12). Permanent flare, in the absence of a cellular response, typically occurs because of multiple ocular surgeries or recurrent, chronic anterior uveitis. Flare does not require treatment unless some associated sign of active ocular inflammation is present.

Iris

Large accumulations of inflammatory cells on the surface of the iris are known as iris nodules. Koeppe nodules form on the pupillary border and Busacca nodules form on the ciliary portion of the iris. The presence of nodules increases the likelihood of an associated granulomatous systemic disease.

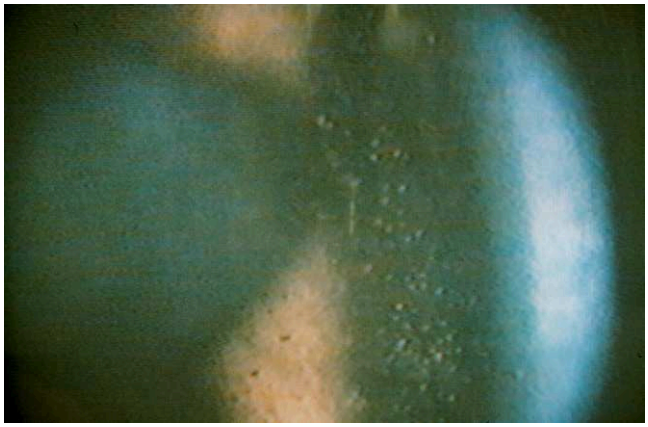

FIGURE 21-10 ■ Plastic iritis. This severe, acute, nongranulomatous uveitis has flare caused by high fibrin content in the aqueous with Grade 4 cells.

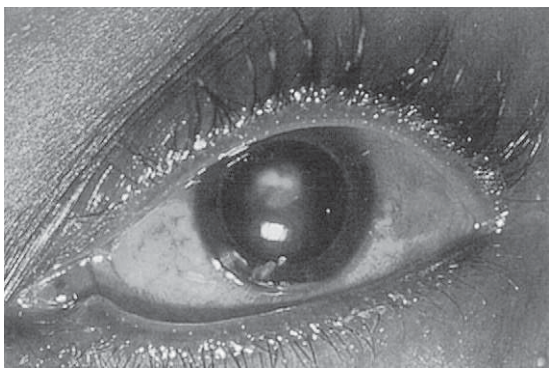

FIGURE 21-11 ■ Hypopyon. Note the subtle area of hypopyon at the most inferior aspect of the anterior chamber. (Courtesy Jane Stein.)

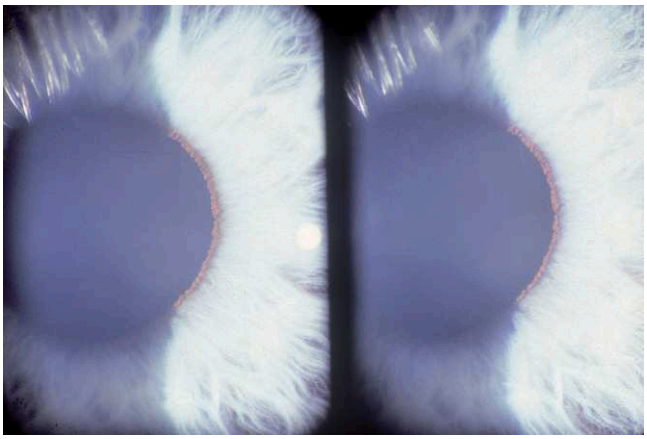

FIGURE 21-12 ■ Flare in the anterior chamber. The bright light reflex on the left is the cornea and on the right is the iris. The normally invisible aqueous is visible as a hazy band extending through the anterior chamber.

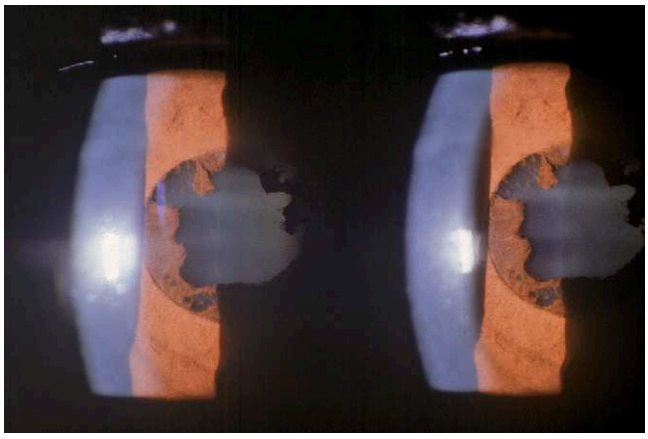

FIGURE 21-13 ■ Posterior synechiae. These adhesions between the iris and anterior lens surface can cause pupil distortion and block aqueous flow into the anterior chamber.

Anterior synechiae, an abnormal connection between the anterior peripheral iris to the peripheral corneal endothelium, may occur because of iris swelling in anterior uveitis. The iris swells because of the inflammation in the anteroposterior axis, thus narrowing the angle of the eye. In extreme and rare cases, the angle may close and cause an acute closed-angle glaucoma attack secondary to the iritis. The synechiae represents a semipermanent adhesion between the iris and cornea, mostly caused by the presence of fibrin acting as biological glue. Breaking of the anterior synechiae may be accomplished with laser therapy or a surgical approach. Any case of anterior uveitis with elevated IOPs mandates a gonioscopic evaluation of the angles to confirm the presence of anterior synechiae.

Posterior synechiae forms much more often than anterior synechiae in cases of anterior uveitis. Here, an adhesion occurs between the iris and the anterior lens surface, most commonly along the pupillary border of the iris (Figure 21-13). The presence of Koeppe nodules increases the chance of posterior synechiae formation, because fibrin binds the nodule to the anterior lens capsule. Posterior synechiae most commonly occurs in granulomatous reactions of the anterior chamber. The adhesion can usually be broken within the first 72 hours of formation by using strong dilating and cycloplegia agents. After 3 days the pharmacological splitting of a posterior synechiae becomes problematic. Although the synechiae does not represent a significant problem to the functioning of the eye, it may cause a distorted pupil, reduce pupillary functioning, and be cosmetically unappealing. Extensive posterior synechiae may bind down the entire pupil leading to pupillary block with iris bombe. As the iris is pushed anterior by accumulating aqueous behind it, the angle may close down leading to an acute angle-closure glaucoma attack secondary to pupillary block. An emergency laser peripheral iridectomy may be necessary to allow appropriate aqueous drainage from the posterior chamber and restore normal angle anatomy. The presence of posterior synechiae increases the chance of further adhesions should the uveitis reoccur. Therefore, it is imperative to attempt to break any posterior synechiae that is discovered.

Synechiae are considered a complication of anterior uveitis, and because they are often associated with granulomatous disease and iris nodules, their presence increases the likelihood of an associated systemic disease.

Anterior Chamber Angle

In addition to anterior synechiae, iris neovascularization may be associated with anterior uveitis. Also, an intraocular tumor of the angle or a ciliary body mass may cause a uniocular uveitis. Because of these entities, a gonioscopic evaluation of the angle is imperative in all cases of anterior uveitis.

Lens

Anterior uveitis increases the risk of cataract development caused by a change in normal intraocular physiology. In addition, the use of corticosteroids is associated with the development of subcapsular cataract (Figure 21-14). Lens opacities associated with uveitis are not seen as a marker for systemic disease, but this condition can hinder evaluation of the fundus. In some cases of systemic disease-related uveitis, a retinal evaluation is mandatory to help diagnosis. In some extreme cases, cataract removal is essential to determine whether the patient should be on immunosuppressive therapy.

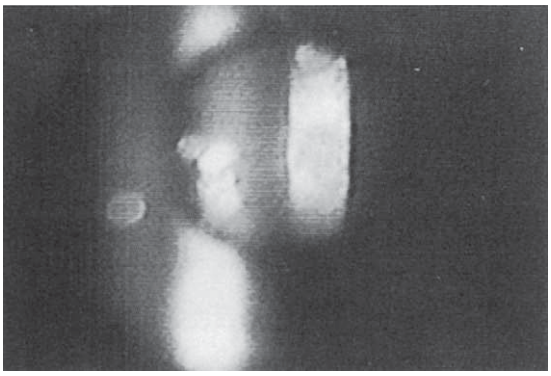

FIGURE 21-14 ■ Posterior subcapsular cataract in a patient on long-term use of corticosteroids for chronic uveitis.

Vitreous

White blood cells arise in the vitreous from the choroid, retina, and ciliary body. Protein can also leach into the vitreous, producing a haze. Vitreous haze is a better indicator of inflammation than cells are and is best seen in a binocular indirect view. Inflammation of the vitreous, or vitritis, indicates a posterior extension of the uveitis, and is therefore more likely to be associated with a systemic disease. The classic appearance of a vitritis is that of a "headlight in a fog," because the yellow optic nerve head surrounded by a pinkish-red blurry fundus weakly reflects the examiner's light. Typically, little or no fundus detail can be visualized through the hazy vitreous.

Retina

The deposition of accumulations of white blood cells along the pars plana is known as "snowballs" and is often associated with systemic diseases, particularly Lyme disease. This form of intermediate uveitis is often found concurrent with anterior uveitis.

The snowballs are best seen with a binocular indirect ophthalmoscopic evaluation of the fundus. Snowballs have also been reported with uveitis secondary to tuberculosis.

Sheathing of the peripheral retinal vessels reflects an inflammatory response within the vessel walls. The presence of sheathed retinal vessels associated with an anterior uveitis increases the likelihood of a systemic disease, particularly syphilis or sarcoidosis. In the case of sarcoid, the vessels take on the classic appearance of "candle-wax drippings."

Optic Nerve Head

Disc hyperemia, papillitis, and papilledema can be associated with anterior uveitis. The finding of any of these optic nerve head changes greatly increases the likelihood of the anterior uveitis being associated with a systemic disease. For example, sarcoidosis can directly affect the nerve head, which may swell, either because of granulomatous deposition within the optic nerve or an increase in intracranial cerebrospinal fluid pressure (Figure 21-15).

TREATMENT OF ANTERIOR UVEITIS

The medical intervention required to treat anterior uveitis is guided by three goals. The first and foremost goal is the reduction and eventual elimination of the intraocular inflammation. Timely intervention reduces the chance of serious complications such as massive KP formation, cataract, glaucoma, and permanent visual reduction.

The second goal involves the mitigation of the pain and photophobia associated with anterior uveitis. The ocular irritation associated with intraocular inflammation is of significant concern and should not be overlooked. Symptomatic relief is an ethical imperative of appropriate therapeusis. The alleviation of photophobia also helps promote the doctor-patient interpersonal relationship and improves compliance.

Finally, the clinician must attempt to prevent formation of posterior synechiae and break any existing adhesions. This reduces the possibility of permanent pupil dysfunction and prevents future episodes of pupillary-block glaucoma.

Mitigation of Inflammation

Amelioration of the inflammatory response is the primary goal of uveitis therapy. The inflammatory response of anterior uveitis is an undesirable derangement of the immune response that can lead to permanent intraocular scarring and visual loss. By quelling this exaggerated response, the risks of such complications are greatly reduced.

In the natural world, anterior uveitis evolved as a way to protect the eyes and body from invasion by

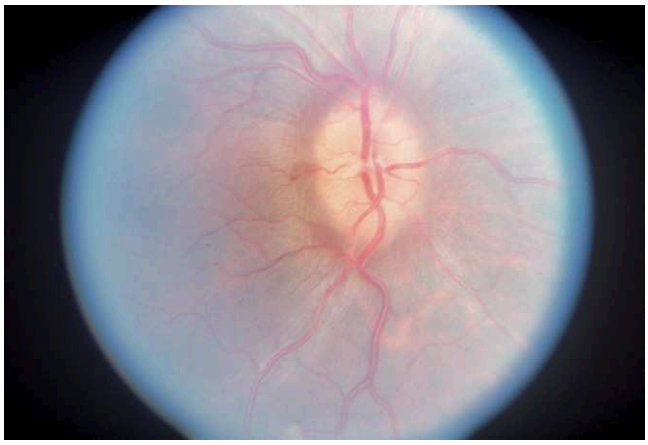

FIGURE 21-15 ■ Papilledema in a case of sarcoidosis. Note the blurry margin of the disc.

dangerous pathogens. Intraocular organisms could easily invade the bloodstream to infect all parts of the body. Any sight-threatening complication of the anterior uveitis was overridden by the potential life-saving response of the ocular immune system. Modern medical intervention makes obsolete this hairpin response by the iris and ciliary body. Anterior uveitis no longer is considered an advantageous immune response, because it can cause such devastating ocular complications. Therefore, treatment of anterior uveitis reduces the risk of such complications without an associated rise in morbidity or mortality.

The anterior uveitis response is characterized by iris and ciliary body blood vessel dilation, degranulation of mast cells with bradykinin and histamine release, and lymphocyte proliferation. Topical corticosteroid eyedrops act to reduce the intraocular inflammation by stabilizing both the capillary bed and the mast cell membrane and reducing white blood cell proliferation.

Typically, therapy with topical steroid drops is started by using one drop every hour on the first day as a loading dose in the affected eye. On the second day, this schedule is usually tapered to every other hour during waking hours. On the third day, as some cellular clearing is usually observed in the anterior chamber, the drop is titrated to four times daily. The steroid drop is tapered slowly during the next 2 to 3 weeks.

Topical corticosteroids run the risk of glaucoma, cataract formation, and poor corneal wound healing. The patient should be monitored for these complications during the course of the treatment at least once weekly.

Oral steroids have been used in some profuse anterior uveitis reactions, but are usually not necessary.

Symptomatic Relief

Photophobia is of primary concern to the patient. This aversion to light is a symptom usually not previously experienced and can be frightening to the patient. Photophobia is stressful and typically overrides all other concerns of the patient.

Photophobia is produced by the biochemical cascade that is responsible for the inflammatory response of the eye. As the iris swells, the threshold to pain of the iris nerve is reduced. Any movement of the iris will now produce pain. When the eye is exposed to light, the pupil quickly constricts and the irritation and pain that results can be unbearable.

Photophobia may have evolved to play a role in the adaptive response of the organism to intraocular inflammation. An organism challenged with such inflammation responds to photophobia by seeking out a dark environment, thus allowing for pupil dilation and iris stability. This in a sense produces a natural cycloplegia without pharmacological blockade of the pupil and helps speed the resolution of the uveitis.

Cycloplegia acts to paralyze the sphincter muscle by use of a parasympatholytic agent that renders the iris immobile and dilated. Preventing movement of the iris ameliorates photophobia, and the patient is provided with symptomatic relief.

Pain can help initiate the inflammatory response, and although cycloplegia does not exert an antiinflammatory effect, the reduction in photophobia may prevent an exacerbation of the uveitis.

The spectrum of cycloplegic agents runs the gamut from 1.0% tropicamide (Mydriacyl) , an effective dilator but poor cycloplegic agent, to 1.0% atropine, a poor dilator but the most effective of all cycloplegic agents. The best choice of cycloplegic agents is 0.5% homatropine, a topical medication affording both excellent dilation and cycloplegic effects. Atropine provides for superb cycloplegia, but immobilizes the pupil in the middilated position. In this position the iris is closest to the anterior lens capsule, where it is most vulnerable to pupillary block and posterior synechiae formation.

In most cases of anterior uveitis, the appropriate cycloplegic agent is homatropine 5.0%, used twice daily. It may be stopped without tapering once clearance of the anterior chamber cells is appreciated. Usually this occurs with treatment in 3 to 4 days. Atropine is often used in acute iritis with a profuse cellular response that is accompanied by fibrin or hypopyon production, but in such cases a topical sympathomimetic should be used concurrently to provide maximal pupillary dilation.

Posterior Synechiae Intervention

Posterior synechiae represent an abnormal adhesion between the iris and lens. The further away the iris is from the anterior lens surface, the less the chance of synechiae formation. The iris is furthest from the lens when it is in the dilated position.

Mydriasis is provided by stimulation of the iris dilator muscle with a sympathomimetic medication. Topical 2.5% phenylephrine is most often used twice daily to accomplish the goal of preventing posterior synechiae formation. The medication is usually discontinued as soon as cellular clearing is observed in the anterior chamber; the dilating agent need not be titrated.

Posterior synechiae may be broken by use of 2.5% or 10.0% topical phenylephrine within 3 days of formation. Thereafter it becomes more difficult to break existing synechiae. The 2.5% formulation of phenylephrine has a lower success rate of breaking existing synechiae, but is a safer medication to use than the more potent 10.0% formulation. However, 10.0% phenylephrine may have significant cardiogenic side effects, including tachycardia, and is associated with more adverse sequelae than the 2.5% concentration. Because of these untoward side effects, 10% phenylephrine is safest

when used only in the office. Punctal occlusion will limit systemic absorption of this potent sympathomimetic medication and minimize the potential of an adverse reaction.

Resistance to Treatment

With treatment, cell clearing from the anterior chamber usually can be observed within 3 days of the initiation of drops. Most cases of uveitis resolve completely in 2 to 3 weeks. Resistance to drug therapy causes an extension of the clearing time, with persistence of photophobia and cells well past a month. The uveitis should be considered chronic if it persists past 6 weeks despite treatment. Resistance to drug therapy is a strong indicator of an underlying systemic disease as a cause of the anterior uveitis.

When the anterior uveitis is becoming obviously chronic, an alternative to topical steroid drops is the use of a periocular corticosteroid injection. This method permits a relatively high concentration of steroid to be given rapidly. Adverse sequelae to this route of administration include accidental globe perforation, proptosis, and fibrosis of the extraocular muscles, severe glaucoma, and the need in children to perform this procedure under general anesthesia.

Although oral steroids have been used concurrently with topical steroid drops in the treatment of anterior uveitis, it is doubtful that systemic corticosteroids play a significant role in the amelioration of intraorbital inflammation. Higher concentrations of steroid are achieved in the eye by use of topical drops than by oral administration. Systemic corticosteroids are the initial drug of choice, however, when treating severe bilateral idiopathic uveitis that is threatening the sight of the patient. In these cases, the treating clinician should make every effort to rule out the possibility of malignant disease or infection as a cause of the anterior uveitis. In addition to this instance, an anterior uveitis caused by Behçet's disease is most effectively treated with oral steroids (Figure 21-16).

Recurrent Anterior Uveitis

An anterior uveitis that recurs after cessation of treatment is at a higher risk of being associated with a systemic disease than a single episode of intraocular inflammation.

Recurrent anterior uveitis requires more aggressive treatment and a longer duration and tapering of topical corticosteroids than a first-time presentation. In general, the reappearance of anterior uveitis demands a longer treatment period, often twice as long, as the initial case. In recurrent cases tapering of the steroid is prolonged by many more weeks and compliance by the patient becomes a serious issue.

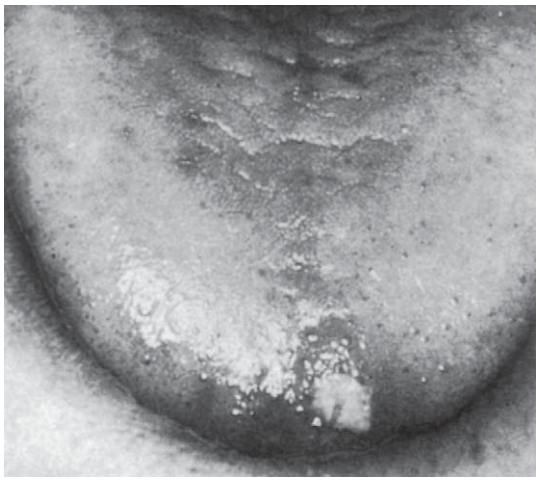

FIGURE 21-16 ■ Behçet's syndrome. Several painful ulcers on the tongue. These may be recurrent for years. (From Cawson RA, et al: *Pathology: the mechanisms of disease,* St Louis, 1989, Mosby Year-Book.)

Recalcitrant cases of anterior uveitis may require a low-dose daily regimen of one drop of topical steroid every day or every other day for the rest of the patient's life in order to quell the inflammation. Every attempt should be made in these cases to ascertain the underlying cause of such chronic inflammation.

ANTERIOR UVEITIS AND SYSTEMIC DISEASE

Systemic Disease–Related Uveitis Characteristics

Any recurrent anterior uveitis should be suspected of having an associated systemic disease as an underlying cause.

First-time cases of intraocular inflammation may have tell-tale primary characteristics that raise the suspicion of systemic disease and instigate laboratory investigation. These characteristics include a uveitis that extends into the posterior chamber, is chronic in nature, bilateral, and resistant to treatment.

Secondary characteristics include the presence of granulomatous keratic precipitates, hypopyon, iris nodules, posterior synechiae, posterior chamber cells, "snowballs" on the pars plana, macular edema, and disc edema. In addition, the presence of any systemic symptoms such as fever, joint pain, malaise, and lymphadenopathy concurrent with uveitis raises the suspicion of systemic disease.

General Disease Classification

Nine systemic diseases are far more commonly associated with anterior diseases than all others. These nine are classified into three groups of diseases: the collagen-

vascular diseases, the inflammatory diseases, and the infectious diseases (Table 21-1).

The collagen-vascular diseases are a group of disorders characterized by the presence of joint pain and inflammation, the underlying cause of which is typically idiopathic, although infectious sources have been identified for certain rheumatological entities. Typical of many of the collagen-vascular diseases that cause uveitis is the presence of the HLA-B27 haplotype. These disorders include ankylosing spondylitis, Reiter's syndrome, juvenile rheumatoid arthritis, and Crohn's disease. The characterization of diseases is complicated by shared characteristics and etiologies. For example, Lyme disease is a non–HLA-B27 infectious disease caused by a bacterium, but it can cause significant collagen-vascular joint pain and inflammation.

The second class of anterior uveitis-related systemic disease includes the inflammatory conditions of sarcoidosis and Crohn's disease. These conditions have no known infectious source and are of unknown etiology, but have inflammation as the primary pathologic characteristic. Note that Crohn's disease can be considered both an inflammatory condition of unknown etiology, and an HLA-B27–related disorder.

The third class of disorders is infectious diseases. The most common infectious diseases that cause anterior uveitis are tuberculosis, Lyme disease, syphilis, and the herpes viruses.

Collagen-Vascular Diseases

Ankylosing Spondylitis

A collagen-vascular, HLA-B27–related disease, ankylosing spondylitis (AS) is characterized by inflammation of the sacroiliac joints, total spinal fusion, back pain and stiffness. AS typically occurs in white males, 20 to 40 years of age, who early in the course of the disease begin to notice lower back pain. Early diagnosis and treatment is essential to prevent permanent spinal deformity. Of patients with AS, 25% have some sort of ocular involvement, including iritis. The inflammation is typically acute, unilateral, painful, and confined to the anterior chamber. There may be fibrin deposition with development of a hypopyon. The pupil may become occluded with a fibrous membrane and visual acuity may drop to light perception (Figure 21-17). Ocular treatment frequently involves the use of topical atropine with dilating agents and topical corticosteroid drops. Because 96% of patients with AS have the HLA-B27 antigen, laboratory testing for this haplotype is essential. Other laboratory tests for AS include radiographs for the sacroiliac joints to rule out sacroiliitis, and rheumatoid factor, which should be negative. Treatment of AS includes nonsteroidal antiinflammatory drugs (NSAIDs) and physical therapy. Any patient who is seen with an anterior uveitis and lower back pain should be screened for AS.

Reiter's Syndrome

An HLA-B27 disorder, Reiter's syndrome (RS) is characterized by arthritis, uveitis, and urethritis. RS occurs most often in white males aged 20 to 40 years. Dermatological lesions may erupt on the skin in association with RS. The most common location of the arthritis in RS is the wrist and ankles. The diagnosis is made on the basis of the clinical signs associated with a positive HLA-B27 test. The uveitis is treated with topical agents and is usually fairly mild, although corneal "meltdown'" has occurred in some cases. The systemic condition is controlled with NSAIDs and immunosuppressive therapy. Any patient with an anterior uveitis and distal joint pain should be screened for Reiter's syndrome.

Juvenile Rheumatoid Arthritis

The diagnosis of juvenile rheumatoid arthritis (JRA) is made on the basis of the presence of arthritis in a child younger than 16 years with no known etiology. There is usually a negative rheumatoid factor (RF) test. Several subclassifications of JRA exist, but in general young girls are much more susceptible to the disease than young boys. The most commonly inflamed joint in JRA is the knee, although children may not complain of pain. Usually a significant asymmetry will be noted when the appearance of the two knees is compared. Laboratory tests, including joint film, RF, ANA, and a WBC will help confirm the diagnosis. Of boys with pauciarticular JRA, 75% are positive for the HLA-B27 antigen, and girls tend to be negative for this antigen. Treatment of JRA may include systemic steroids and surgery. The highest risk of anterior uveitis in JRA occurs in girls with pauciarticular arthritis who test positive for ANA. The anterior uveitis associated with JRA is typically chronic and asymptomatic. The uveitis is often picked up on routine examination, by which time severe intraocular damage has already occurred. Usually no conjunctival injection is present, but a cellular anterior chamber response has caused posterior synechiae formation and pupil distortion (Figure 21-18). A band-shaped keratopathy occurs in more than half the patients, and may lead to visual disturbance (Figure 21-19). Cataract and glaucoma can result in chronic JRA-related uveitis. Topical corticosteroids are the mainstay of treatment and young JRA patients need to be seen every 3 to 4 months. Intraocular injections of steroid may be needed to quell the intraocular inflammation, but general anesthesia is necessary in children to accomplish this procedure. Oral steroids should be avoided in children for JRA-related uveitis, because these drugs have overwhelming side effects on bone growth. Eventual cataract extraction may be needed to allow for appropriate visual stimulation and prevention of amblyopia in the arthritic child. Of all patients with severe JRA-associated iridocyclitis, three quarters

TABLE 21-1 OCULAR FINDINGS

SYSTEMIC DISEASE CAUSING UVEITIS	CLASS	PRIMARY SYSTEM AFFECTED	PATH	ET	AGE
Ankylosing spondylitis	Collagen Vascular	Lower vertebrae	Bony fusion	Possible genetic infection association	Young adult
Reiter's syndrome	Collagen Vascular	Bone joints	Arthritis	Possible genetic infection association	Young adult
Juvenile rheumatoid arthritis	Collagen Vascular	Joints (knee)	Arthritis	Unknown autoimmune	<16 yr
Crohn's disease	Inflammatory	GI	Ulcers and granulomas	Possible genetic association	20-40 yr
Sarcoidosis	Inflammatory	Pulmonary	Granulomas	Immune response to airborne antigen	20-50
Lyme disease	Infectious	Multi Derm Cardiac Arthritis	Inflammatory, infection, and immune	*Borrelia burgdorferi* (spirocheta)	Any age
Syphilis	Infectious	Multi Derm Neuro	Inflammatory and infection	*Treponema pallidum* (spirochete)	Any age
Tuberculosis	Infectious	Pulmonary	Bacterial infection	Tubercle bacilli	Any age
Herpetic disease	Infectious	Multi (derm)	Viral infection	DNA virus	Any age

GI, Gastrointestinal; *RF,* rheumatoid factor; *ESR,* erythrocyte sedimentation rate; *ANA,* antinuclear antibody; *ACE,* angiotensin converting enzyme; *ELISA,* enzyme-linked immunosorbent assay; *FTA-ABS,* fluorescent treponemal absorbed; *MHA-TP,* microhemagglutination-*Treponema pallidum; VDRL,* Venereal Disease Research Laboratory; *RPR,* rapid plasmin reagin; *PPD,* purified protein derivation; *HIV,* human immunodeficiency virus; *NSAID,* nonsteroidal antiinflammatory drug; *INH,* isoniazid.

demonstrate a band-shaped keratopathy. The keratopathy can be removed with chemical chelation. The excimer laser may play a role in removal of the band-shaped keratopathy in the future. Every child with anterior uveitis must be screened for JRA.

Inflammatory Diseases

Sarcoidosis

Sarcoid is a multisystem granulomatous disease of unknown etiology. This disease can affect almost any organ system in the body, although the usual involvement is the lungs and skin. The highest incidence of sarcoid in the world is found in Sweden. In the United States, an even higher level is found in African-Americans, but a very low rate is found in the white population. Commonly in the United States, the sarcoid patient will be a young, African-American female, aged 20 to 40 years, who is often asymptomatic. If systemic symptoms are present, most patients with sarcoid present with coughing, fever, fatigue, and weight loss. Laboratory tests for sarcoid include, among others, a chest x-ray (demonstrating a hilar adenopathy), gallium scan, angiotensin-

SEX	RACE	KEY SYMPTOMS	KEY LAB TESTS	SYSTEMIC TREATMENT	POSSIBLE SEQUELAE
M > F	W > B	Lower back pain	HLA-B27 X-ray back RF (−) ESR (+)	Steroids NSAID Physical therapy Self limits in 2 years or more	Limited mobility of back and legs
M > F	W > B	Arthritis Urethritis Conjunctivitis	HLA-B27 ESR (+) ANA (−) RF (−) Urethral swab	Steroids NSAID Self limiting	Advanced arthritis: corneal "meltdown"
M < F	W = B	Knee pain	X-ray knee RF (−) ANA (+)	Steroids NSAID Immunosuppressants	Phthisis bulbi: knee joint immobility
M = F	W = B	Gut pain	GI workup Endoscopy Rectal biopsy Barium enema HLA-B27	Steroids Diet Surgery Stress reduction	Severe GI complications
M < F	W < B	Cough	Biopsy lung Biopsy conj. nodule ACE-elevated Galium scan of lung (chest x-ray)	Steroid therapy	5% mortality (death rate); respiratory distress
M = F	W = B	Rash Fever Arthritis	ELISA (+) for antispirochetal Antibody titer	Antibiotics: tetracycline or doxycycline or amoxicillin	Advanced cardiopathy and neuropathy
M = F	W = B	Rash Fever Chancre	FTA-ABS or MHA-TP VDRL or RPR	Systemic antibodies	Tertiary stage with neuropathy
M = F	W = B	Cough	PPD Mantoux X-ray chest Sputum culture	INH-isoniazid	Lung excavations and cavaties
M = F	W = B	Skin vesicles	Skin biopsy Skin culture Consider HIV testing	Oral acyclovir	Postherpetic neuralgia: cataract

converting enzyme (ACE), serum lysozyme, and a positive skin (Figure 21-20) or lung biopsy. Of sarcoid patients, two thirds develop anterior uveitis, typically an acute iridocyclitis. The intraocular inflammation is characterized by granulomatous keratic precipitates and iris nodules. Eventually, peripheral retinal blood vessel sheathing, a white inflammatory response known as "candle-wax dripping," may occur. The uveitis may be associated with disc edema or papilledema, as granulomatous sarcoid nodules invade the optic nerve or interfere with cerebrospinal fluid drainage. Often, systemic sarcoid does not require treatment unless significant symptoms are present. Corticosteroids are the mainstay of treatment for both systemic and ocular sarcoid. Any patient with anterior uveitis who has a chronic cough should be evaluated for sarcoidosis.

Crohn's Disease

Of patients with Crohn's disease, 50% are HLA-B27 positive. This inflammatory bowel disorder has been associated with the deposition of granulomatous nodules from the tongue to the rectum. The uveitis associated

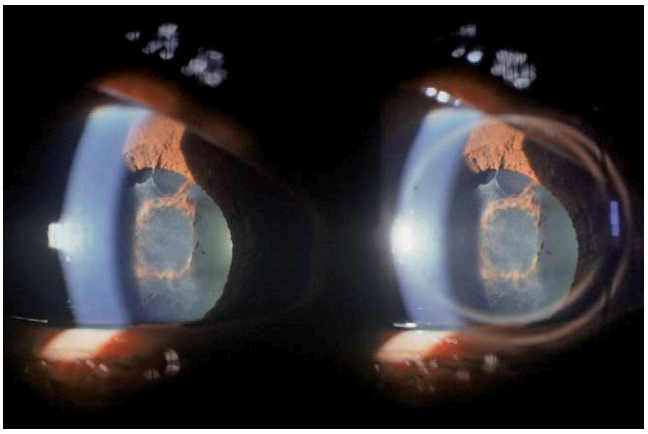

FIGURE 21-17 ■ Acute plasmoid iridocyclitis in a patient with ankylosing spondylitis. Note the high fibrin content on the aqueous around the pupil.

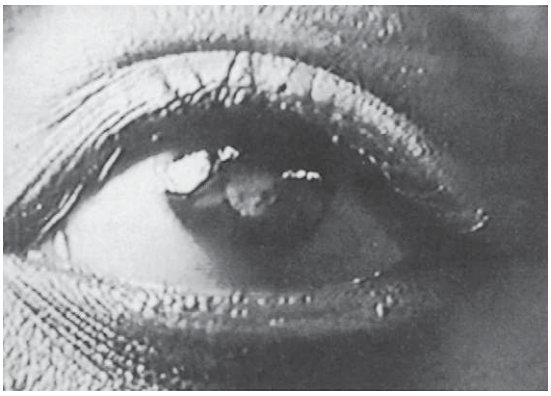

FIGURE 21-18 ■ Iridocyclitis in a patient with juvenile rheumatoid arthritis revealing a "white" pupil caused by a cataract and a distorted pupil secondary to posterior synechiae.

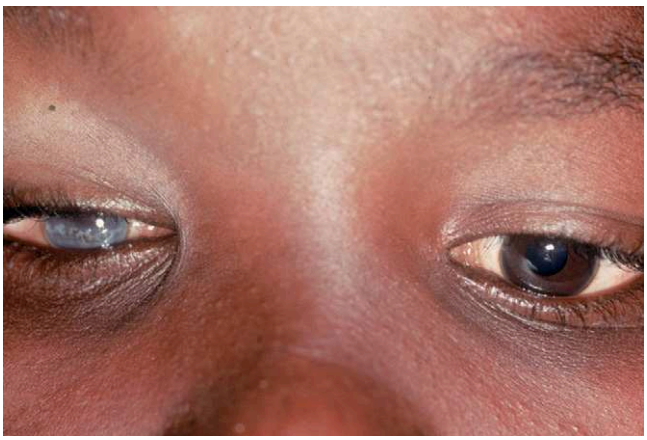

FIGURE 21-19 ■ Band keratopathy. Calcium deposits in Bowman's layer of the cornea in juvenile rheumatoid arthritis.

with Crohn's disease may be granulomatous in nature and have characteristic "mutton fat" KP deposition. Diagnosis of Crohn's disease involves upper and lower GI series, sigmoidoscopy, endoscopy, barium enema testing, hypoproteinemia on blood testing, and symptomology. Any anterior uveitis patient with a history of recurrent diarrhea, bloody diarrhea, or abdominal cramping should be evaluated for Crohn's disease.

Infectious Diseases

Tuberculosis

An infectious disease, tuberculosis (TB) is spread by aerosolized droplets that contain *Mycobacterium tuberculosis.* Inhalation of the bacteria causes a short-lived asymptomatic and self-limited pneumonia. Healing occurs with formation of pulmonary granulomas that calcify and remain inactive. Reactivation of the disease occurs with a second challenge of bacteria, other disease states or age. Approximately 1% of TB cases develop ocular manifestations, and granulomatous anterior uveitis may occur. Diagnosis of TB can be difficult to make and includes a chest x-ray, purified protein derivative (PPD) skin test, and sputum culture. Treatment of systemic TB includes regimens of isoniazid and rifampin for 9 months, with a third drug such as ethambutol for the first 3 months. TB should be suspected in any patient with an anterior uveitis coincident with a chronic cough.

Syphilis

Syphilis is still the most common of all the treponemal infections and the most significant seen in the optometrist's office. The infection is caused by the spirochete *Treponema pallidum* and is transmitted exclusively by sexual contact. Syphilis is characterized by three stages: primary syphilis (stage one) characterized by a chancre, secondary syphilis that often presents with a generalized rash (Figure 21-21), and tertiary, or cardiovascular or neurosyphilis. Syphilis is contagious in the untreated primary or secondary stages, especially if there is mucocutaneous involvement. Late secondary or tertiary syphilis tends not to be infectious. The spirochete cannot live long outside the body and can penetrate intact mucous membranes or abraded skin. The average incubation period is 3 weeks, but can last from 1 week to 3 months. The infection spreads throughout the body through the lymphatic system to the bloodstream. In the eye, anterior uveitis occurs in the secondary and tertiary stages of syphilis. The inflammation of secondary syphilis is typically an iridocyclitis with iris nodules. Laboratory screening for syphilis include the venereal disease research laboratory (VDRL) or rapid plasma regain (RPR) tests. Treponemal tests to confirm any positive screening result include the *T. Pallidum* immobilization test (TPI) and the more com-

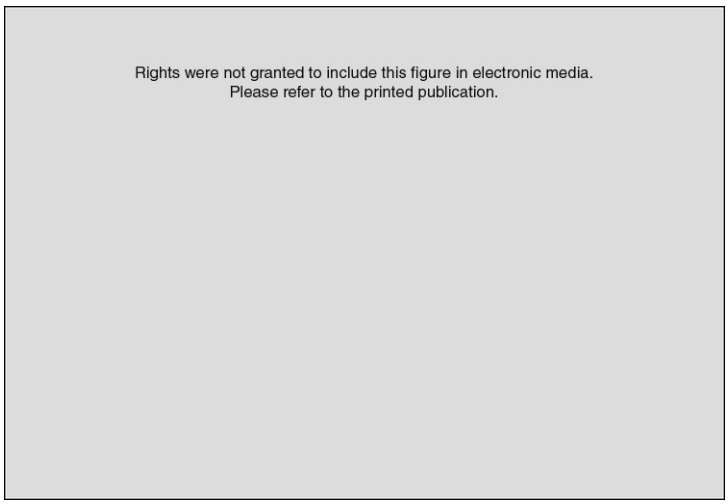

FIGURE 21-20 ■ Sarcoid nodules of the skin. (From Lawrence CM, Cox NH: *Physical signs in dermatology: color atlas and text,* London, 1993, Wolfe Medical.)

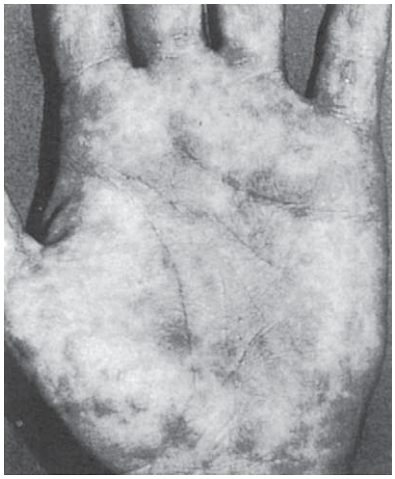

FIGURE 21-21 ■ Syphilis. Maculopapular rash of the palms is suggestive of syphilis. (From Cawson RA, et al: *Pathology: The mechanisms of disease,* St Louis, 1989, Mosby-Year Book.)

mon fluorescent treponemal antibody absorption (FTA-ABS) test. The TPI is expensive, and the microhemagglutination (MHA-TP) test is used less frequently than the FTA-ABS test. Penicillin is the mainstay of treatment in all cases of syphilis, although the amount and route of administration depends on the stage of the infection. In all cases of syphilis, the possibility of coinfection with HIV must be ruled out. Patients with anterior uveitis who have a coincident skin rash should be evaluated for syphilis.

Lyme Disease

This bacterial infection is caused by *Borrelia burgdorferi,* a tick-borne spirochete similar to *T. pallidum.* The spirochete is most commonly found in the Ixodes ticks, whose host is frequently the white-footed mouse (in its larval stage), or white-tailed deer (in the adult stage). Similar to syphilis, the clinical manifestations of Lyme disease are divided into three stages. Stage I involves a local reaction to the tick bite with an accompanying oval erythematous rash that persists for a month. Stage II comprises a disseminated response to any organ system with a host of signs and symptoms, including cardiac and neurological complications. Stage III involves the development of arthritis, chronic fatigue, and dementia. Laboratory confirmation of an infection includes the immunofluorescent assay test (IFA) and enzyme-linked immunosorbent assay test (ELISA) with a confirmatory Western blot test. Laboratory testing still lacks sensitivity in diagnosing Lyme disease and the results should be integrated with the history and clinical signs and symptoms. An FTA-ABS should be used to rule out syphilis as part of the differential diagnosis. The treatment of Lyme disease includes the use of an antibiotic such as oral tetracycline, doxycycline, or amoxicillin. In severe cases, intravenous ceftriaxone or penicillin may be used if prolonged treatment is anticipated. The anterior uveitis associated with Lyme disease is typically an intermediate uveitis or an iridocyclitis with an associated pars planitis. Inflammatory deposits will occur along the pars plana that take on the appearance of "snowballs'" which may rise and fall in the vitreous when the patient looks up and down. Treatment of the anterior segment inflammation caused by Lyme disease consists of topical corticosteroids and cycloplegic agents. Lyme disease should be suspected in any patient with anterior uveitis, particularly a pars planitis, with an associated rash.

Herpes Zoster Ophthalmicus

A DNA herpes virus, herpes zoster ophthalmicus (HZO) remains latent in the ganglia after a patient has had a bout of chickenpox. After reactivation, caused

by secondary infection, environmental stress, or age, the virus travels along the ophthalmic division of the trigeminal nerve. The hemicranial, cutaneous outbreak is vesicular in nature and extremely painful. The lesions are fluid-filled and erupt onto the surface of the skin. Eventually, the skin lesions scab over, become crusty, and flake off the skin surface. Superficial permanent scarring of the skin may result from a single outbreak and cause anxiety and depression in individuals. Postherpetic neuralgia can result in intractable pain after an episode of HZO and require the use of pain-killing medications and antidepressants on a long-term basis. The typical corneal lesion in HZO is a stromal keratitis. HZO can cause vascular occlusion and secondary ischemia of the iris that leads to anterior uveitis. The iris may reveal patchy atrophy that is associated with ischemic areas. Severe ischemia of the iris and ciliary body may lead to phthisis bulbi. The intraocular inflammation associated with HZO keratitis is typified by large KPs and posterior synechiae that develop within 1 to 2 weeks. Histological studies confirm a granulomatous response of the iris and ciliary body. Treatment of HZO should be started within 3 days of the outbreak of HZO with use of oral acyclovir or famciclovir, to reduce virus proliferation, lower the risk of complications, and ease the accompanying intraocular inflammation. Oral antivirals will not mitigate anterior uveitis late in HZO, however, because prolonged intraocular inflammation is caused by ischemia and not viral proliferation. If iris and ciliary body ischemia are present topical corticosteroids and cycloplegic agents may be needed for months to ameliorate the anterior uveitis. Therefore, HZO should be suspected in any patient with anterior uveitis with an associated keratitis and skin outbreak.

Herpes Simplex Keratouveitis

Herpes simplex keratouveitis (HSV) is the most common ocular disease associated with an anterior uveitis. Some uveitis may occur with the epithelial form of the disease, but nearly all stromal keratitis patients have an accompanying anterior uveitis. The inflammation typically causes a very red, painful, and photophobic eye. Slit-lamp evaluation inevitably demonstrates classic dendritic keratitis of the corneal epithelium. Anterior segment involvement usually involves posterior synechiae, anterior chamber cells and KPs posterior to the corneal opacity. The uveitis may be the result of a secondary inflammatory response to the corneal disease or invasion of the virus into the anterior uvea. HSV is treated with topical antiviral agents such as trifluridine (Viroptic) solution or vidarabine (Vira A) ointment. Topical cycloplegic agents should be used to reduce both the associated photophobia and the risk of posterior synechiae development. A topical corticosteroid, particularly prednisolone phosphate, has been shown to reduce persistence or progression of stromal keratitis and improve the time of uveitis resolution. Topical steroid therapy should be started after the corneal epithelial disease is resolved, and should only be used in conjunction with topical antiviral agents. The addition of oral acyclovir is not beneficial in patients with stromal keratitis already receiving topical antiviral agents. Any patient with anterior uveitis and accompanying corneal opacity should be evaluated for HSV infection.

When to Suspect Systemic Disease

Some obvious cases of anterior uveitis warrant a suspicion of an associated systemic disease. All cases of bilateral or alternating anterior uveitis should be evaluated for systemic disease. Recurrent uveitis and cases that resist treatment may have an underlying disease that constantly reinforces the intraocular inflammation. A systemic disease may cause a chronic anterior uveitis with persistence of the intraocular inflammation longer than 4 weeks.

Any iritis that subsequently proceeds posterior to involve the ciliary body, pars plana, vitreous, or retina, is highly suspect for an underlying systemic disease. The uveitis itself may indicate an associated systemic disease if large "mutton-fat" KPs, posterior synechiae, hyphema, hypopyon, or iris nodules are present.

The anterior uveitis least likely to have an associated systemic disease is a first-time unilateral acute iritis with significant circumcorneal flush, photophobia, and small KPs. The level of suspicion is much higher in cases of recurrent, bilateral granulomatous iridocyclitis.

The Uveitic History

In all cases of anterior uveitis, a short history can help screen for the presence of systemic diseases. In general, the patient with anterior uveitis should be asked about associated generalized symptoms including headache, fever, neck pain, swollen lymph nodes, sore throat, malaise, or fatigue. Any associated sign raises the possibility of a systemic disease as the underlying cause of the anterior uveitis.

The patient should then be asked about more specific clinical symptoms associated with the uveitis. The presence of lower back pain, particularly in a young, white male, helps screen for ankylosing spondylitis. Wrist and ankle pain, again in a young, white male, may indicate Reiter's syndrome, especially if an accompanying urethritis is present. Knee pain in a youngster with anterior uveitis, particularly a girl, may indicate JRA, although child abuse must be also considered.

Any pain in the stomach or intestines in a patient with anterior uveitis raises the chances of an associated bowel disorder, particularly Crohn's disease. Other symptoms and signs to ask the patient about include bloody stools, diarrhea, and abdominal cramping.

The patient should be asked about any episodes of coughing associated with the eye inflammation. Pulmonary involvement in these cases may indicate an underlying tuberculosis infection. Sarcoidosis should also be considered in any uveitic patient who reports a chronic cough as this inflammatory condition primarily involves the lungs.

Any report of a rash associated with a uveitis increases the likelihood of syphilis involvement, no matter at the age of the patient. The typical rash in syphilis is on the palms of the hands, soles of the feet, or across the upper back, and is composed of small, maculopapular, red skin lesions. The rash produced in Lyme disease is distinctly different from syphilis, and is typically a single, silver-dollar-sized oval or annular lesion with quickly expanding borders. Any rash associated with an anterior uveitis increases the likelihood of an associated disease.

Laboratory Testing in Anterior Uveitis

If any likelihood exists of an associated systemic disease on the basis of the history or characteristics of the uveitis, laboratory tests can help pinpoint an etiology. A broad laboratory screening can be performed if the uveitis history does not point to a single disorder. The screening should consist of general blood tests as well as specific serology tests for the most common uveitic entities.

The general blood tests include hematology CBC analysis for the WBC (with a differential), RBC, and platelet levels. An erythrocyte sedimentation rate ("sed" rate [ESR]) will help determine whether any body-wide generalized inflammation is present. A blood chemistry panel, such as the SMA-12, may help ascertain any abnormalities in the patient's biochemical profile. Urinalysis is an essential screening for renal dysfunction related to the uveitis.

More specific laboratory tests for inflammation include the rheumatoid factor (RF) to rule out rheumatoid arthritis, antinuclear antibodies (ANA) for JRA, HLA-B27 for the collagen-vascular entities, FTA-ABS and RPR for syphilis, Lyme titer (ELISA), ACE for sarcoid, and PPD and chest x-ray for tuberculosis.

The ordering of laboratory tests is often guided by the associated signs and symptoms in a uveitis patient. Unfortunately, a low yield of valuable information is usually found in the history and examination of the intraocular inflammation. Consequently, laboratory testing in cases of anterior uveitis is often undirected and generalized. In the vast majority of cases of anterior uveitis, laboratory values are normal despite a high suspicion of an underlying disorder. These may represent true undiagnosed systemic disease or a significant insensitivity to the uveitis-associated diseases by established serologic tests.

The ability to diagnose a systemic disease, particularly when the anterior uveitis is the only clinical manifestation of the underlying disorder, allows for early medical intervention, thus minimizing potential complications. This is rewarding for both the patient and clinician, and may preserve the sight and save the life of the patient. However, the inability to diagnose the underlying systemic disease in most cases of anterior uveitis makes this scenario one of the most frustrating in eye care. Sensitivity to the characteristics of uveitis most often associated with an underlying disease, use of the uveitis history, and the frequent use of laboratory tests, should increase the diagnostic yield and permit early medical intervention in cases of systemic disease-related uveitis.

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CHAPTER 22

Posterior Segment Manifestations of Systemic Disease

CHAPTER OUTLINE

When systemic disease affects the posterior segment of the eye, the results can be devastating. Retinal and choroidal scarring can cause permanent visual acuity and visual field loss. Infections, systemic disease, and toxic reactions can cause such extensive histopathological changes that the vision of our patients is inexorably and forever challenged.

Often the first indication of a systemic disease is a posterior segment manifestation detected by funduscopy. All posterior segment lesions should be evaluated for possible systemic disease implications. This chapter details the most significant of the systemic diseases to manifest lesions within the retina and choroids. Included are discussions concerning infections, toxic reactions, hypertensive retinopathy, carotid artery disease, connective tissue diseases, and hematological disorders.

HYPERTENSIVE RETINOPATHY

Systemic Hypertension

Systemic hypertension is classified as a minimum diastolic blood pressure of 85 mm Hg or a minimum systolic blood pressure of 140 mm Hg in a patient older than 50 years. More than 90% of cases of hypertension are idiopathic in nature, with the remainder caused by congenital or acquired renal disease.

Systemic hypertension increases the risk of coronary artery, cerebrovascular, peripheral, vascular, and

renal disease. The impact of such vascular pathologies is reflected in the prevalence of renal failure, strokes, and heart attacks associated with chronic, untreated high blood pressure.

Effects of Systemic Hypertension on Retinal and Choroidal Vasculature

Hypertension induces retinal vascular constriction and eventual sclerosis that can be visualized directly by ophthalmoscopy. Changes in the choroidal vasculature, deep to the retina, cause disturbances in the overlying retinal pigmentary epithelium that can be ophthalmoscopically evaluated. Because hypertensive changes in the vasculature of the posterior segment reflect the effects of chronic high blood pressure and the adequacy and severity of hypertensive control, funduscopic findings may help guide the therapeutic strategy. In particular, the effects of chronic, untreated high blood pressure on the kidneys, central nervous system (CNS), cardiovascular system, and hemopoietic system can be indirectly implied by direct observation of hypertensive changes within the retinal and choroidal blood vessels.

The tissue of the retina reacts to vascular sclerosis in the same way as the tissue of the CNS and cardiovascular system; edema, ischemia, and infarction characterize the resultant vascular ischemia. In a similar way, hypertension causes renal vascular changes that are reflected in the retinal circulation.

Hypertension affects retinal circulation differently than choroidal circulation, because the retinal blood vessels are similar to the blood vessels of the CNS, with a strong blood-retinal barrier maintained by tight cell junctions. Choroidal blood vessels lack these tight junctions, however, and thus an insufficient or nonexistent blood-choroidal barrier is present. Another difference is evidenced by the differences between the retinal and choroidal blood vessels responses to changes in blood pressure, ocular pressure, and blood oxygenation. Retinal blood vessels are characterized by autoregulation in response to these influences, and the choroidal vascular tone is under sympathetic nervous system control. Because of these differences, systemic hypertension will affect the retinal blood vessels differently than the choroidal blood vessels, although the retinal vasculature is most often evaluated because it is easiest to visualize.

It is important to note that the classification of hypertensive retinopathy used to be of prognostic value in helping to determine the effect of systemic hypertension on survival rate. Recent advances in the medical mitigation of hypertension has meant a decreasing role for the classification of hypertensive retinopathy, however, and it is of most value now in determining the effect of hypertension on the circulation of the brain, heart, and kidneys.

Systemic hypertension most commonly affects the small, muscular arteries of the retina, sometimes referred to as retinal "arterioles," but this term may be a histiological misnomer. The space around these retinal arteries, the perivascular space, is small in the young person, and thus the image of the artery is that of a sleek, red tube. With age, however, the perivascular space accumulates smooth muscle cells and glial cells from the basement membrane, and thus an increase in the size of the light reflex occurs. This process of vascular sclerosis is sped up by systemic hypertension.

Although the retinal arteries possess a blood-retina barrier, this may be breached in several disease states, including hypertension. When this breach occurs, a hemorrhage, or leakage of blood, occurs from the site of the break. When this is caused by hypertension, the exudative retinopathy affects the shallow capillaries or arterioles, and the blood spreads out along the nerve fiber layer, taking on the appearance of a flame-shaped hemorrhage.

The Four Phases of Hypertensive Retinopathy

Four phases of hypertensive retinopathy exist, but these phases may not occur sequentially and any phase may occur in isolation. As such, these are not so much stages of hypertensive retinopathy as they are phases.

The Vasoconstrictive Phase

In hypertensive retinopathy, the vasoconstrictive phase is characterized by asymptomatic diffuse and focal constrictions of the precapillary retinal arterioles. This phase is best appreciated using slit-lamp biomicroscopy with red-free illumination. Vasoconstriction is best seen after the second branching of a retinal artery. The vasoconstrictive phase is typically an early, reversible, and treatable stage of hypertension. Blood pressure readings should be taken in the office when the vasoconstrictive phase is discovered, and the patient referred to the family physician for a systemic evaluation.

The Sclerotic Phase

More advanced hypertensive retinopathy results in the sclerotic phase, which rarely develops if the patient with vasoconstriction of the arterioles is promptly treated. These more sclerotic vessels are characterized by a narrowing of their caliber along with a widening of the light reflex, vascular tortuosity, an increase in their angle of branching, and arteriole nicking.

Unfortunately, arteriole narrowing is difficult to quantify, and a comparison of the size of the artery to the vein is not appropriate because the veins may be dilated. Arteriole narrowing may be mild, moderate, or severe.

Arteriovenous crossing changes can occur in the environment of hypertensive retinopathy. These changes have been related to left ventricular hypertrophy. One such change is "nicking," in which a vein underlying an artery is deflected in its course. Mild (slight venous deflection), moderate (venous tapering, constriction or deflection), or severe (impending venous occlusion with hemorrhage and exudates distal to the crossing) nicking may be present. Dilation of the retinal vein distal to the arteriovenous crossing is known as banking, because the blood distal to the crossing is saved like "money in the bank," not because the vein banks, or is deflected, in its course.

Sclerosis of the arterial wall can also develop in the sclerotic phase. This condition produces a widened light reflex compared with the width of the light reflex in the patient without systemic hypertension. Mild sclerosis (mildly increased light reflex), copper wiring, or silver wiring may be present. The copper color is produced by sclerosis that covers the entire anterior surface of the retinal artery. The silver color of advanced sclerosis is produced by thickening and hyalinization of the vessel wall such that the artery looks like a silver cord, although active blood flow may still be present.

With chronic hypertension, an increase in the tortuosity of the retinal arterioles may be present. This must be differentiated from congenital tortuosity, which is a benign condition.

Prolonged hypertension may also produce an increase in the angle of arterial branching, with greater blood pressure producing a larger angle. This angle is best visualized between the second and third arteriole bifurcation. It may be mild (45 degrees to 60 degrees), moderate (60 degrees to 90 degrees), or severe (more than 90 degrees).

The Exudative Phase

The third phase of hypertensive retinopathy is the exudative phase, which is usually accompanied by the vasoconstrictive phase, the sclerotic phase, or both. In the exudative phase, a disruption of the blood-retinal barrier occurs as measured by fluorescein angiography, and a leakage of fluid and blood cells from the circulatory system is present. This results from the inability of the autoregulatory system of the arteriole wall to overcome the perfusion pressure within the arteriole lumen. A consequential breach of the vessel wall occurs with leakage and a disruption of blood flow that results in retinal tissue ischemia. The earliest signs of the exudative phase are flame-shaped hemorrhages that result from leakage of superficial arterioles with spreading of the blood along the nerve fiber layer. If the hemorrhage breaks through the internal limiting membrane, a boat-shaped hemorrhage forms within the subhyaloid space in the posterior pole.

If plasma lipoproteins, triglycerides, and cholesterol leak from the arteriole, then hard, waxy exudates may form. These exudates are bright yellow, form in the posterior pole, and may assume a star-shaped appearance around the macula. This appearance results from the exudates leaking along the nerve fiber layer in a linear fashion, radiating away from the fovea.

Exudation can disrupt blood circulation to such a degree that the resulting lack of oxygenation to the retinal tissues results in ischemia. The whitish-gray or yellow patches of infarcted retinal tissue are known as cotton-wool spots (CWS). CWS most often are produced at right angles to the nerve fiber layer and are superficial to the blood vessels. CWS represent ischemic retinal tissue, as evidenced by fluorescein angiography that will frequently reveal nonperfusion in these areas. Ischemic retinal tissue may produce collaterals to distribute blood flow around the CWS, and the presence of these new blood vessels help to confirm the presence of CWS.

Complications of Sclerosis Phase

The fourth and final stage of hypertensive retinopathy occurs when complications occur because of the sclerotic phase. These complications include vascular occlusions, microaneurysms, and epiretinal membrane formation. In addition, retinal ischemia may lead to neovascularization, vitreous hemorrhage, retinal detachment, and cystoid macular edema. The earliest symptom of these changes is usually a reduction in visual acuity, which normally is unaffected by hypertensive retinopathy because the changes are scattered and peripheral to the macula. In the fourth phase of this retinopathy, however, maculopathy secondary to edema, exudation, or membrane formation can lead to blurred vision.

Malignant hypertension may be considered an end result of the fourth stage of hypertensive retinopathy, wherein the systemic hypertension has produced swelling of the optic nerve head. In his classification scheme, Scheie defined stage four hypertensive retinopathy as the presence of papilledema. Bilateral disc edema, known as papilledema, appears as a disc with blurry margins, a filling of the optic cup, and congested retinal veins. This congestion is the result of an accumulation of axoplasmic debris in the lamina of the optic nerve head, which results in swelling of the axons and leads to disc edema.

Effect of Systemic Treatment on Hypertensive Retinopathy

With treatment of the systemic hypertensive condition, the associated retinopathy may become stabilized or even reversed in some instances. Systemic medical or surgical intervention may reduce the risk of retinal

complications in the sclerotic phase including vascular occlusion and macular involvement. Typically, 6 to 12 months after systemic hypertension control the retinal hemorrhages, exudates, and CWS resolve. Malignant hypertension requires emergency control of the systemic hypertensive condition, and the papilledema usually resolves within weeks.

CAROTID ARTERY DISEASE

The Carotid-Eye Axis

Two major oculovisual ramifications of carotid disease exist. The first occurs when atherosclerosis of the carotid artery causes the formation of emboli that travel either to the eye or brain. On entering the retinal vascular system, the emboli may become lodged in an arterial bifurcation, ultimately yielding a loss of vision caused by arterial occlusion. A carotid artery emboli that leads to the brain may cause symptoms of a transient ischemic attack (TIA), including a variety of visual field defects. A vascular specialist must evaluate the carotid arteries whenever emboli are visualized in the retinal vascular arterial tree.

The second affect of the carotid artery on the eye may occur because of complete stenosis of the vessel that results in ocular ischemic syndrome (OIS). OIS is also known as venous stasis retinopathy.

Retinal Arterial Emboli

Etiology

An embolism represents the presence of a material foreign to the involved blood vessel. In the eye, the most common source of an embolism is from the carotid artery, and the material involved is usually cholesterol, calcium, or fibrin. The embolism most often lodges in a retinal artery that is narrower than the plug of material, or at a bifurcation of an artery. The embolism may be visualized as a brilliant and small white, yellow, or gray pinpoint of light shining from the lumen of a retinal artery. Typically, some blood flow occurs around the obstruction, thus blood may be seen on both sides of the embolus within the lumen of the vessels. Usually, a white embolus represents a plug composed mostly of calcium, a yellow plug is primarily cholesterol, and a gray plug is composed of mostly fibrin. The origin of the plug is typically a thrombus that broke off from the wall of the carotid artery. In all cases of retinal embolism, a coronary source of the material should also be considered, particularly if the plaque is white and therefore composed mostly of calcium.

Symptoms and Signs

The retinal arterial embolism, often termed a Hollenhorst plaque, may cause no symptoms and is often discovered on a routine eye examination. If a symptom occurs associated with the plaque, it is usually a fleeting loss of vision that lasts from seconds to hours. The appearance of multiple emboli over time within the arterial tree produces fleeting losses of vision for seconds at a time. The losses of vision occur because a temporary occlusion of an artery occurs, followed by a breaking up of the embolism, the components of which are taken downstream into the finer capillary system. A larger embolism can become lodged in a vessel permanently and cause massive ischemia to part of the retina, with a concurrent permanent loss of vision or of the visual field. Alternatively, in some cases a large embolism lodges in a vessel and yet produces no symptomology at all. This situation is usually the result of blood flow coursing around the embolus and continuing to supply the retinal tissue.

Systemic Evaluation

The symptomology of the visual TIA, or the discovery of a Hollenhorst plaque on ophthalmoscopy, should instigate a dedicated search for the etiology of the embolism. The optometrist should draw or photograph the embolism for documentation purposes. Next, auscultation of both carotid arteries should be undertaken to search for a thrombus that produces a bruit. The bruit is a "whooshing" sound heard between the quick beats of the heart and represents irregular blood flow around a thrombus. On pinpointing a bruit in a carotid artery, the optometrist should draw in indelible ink a circle around the side on the neck of the patient. This will locate the bruit for the family physician and is necessary, because the bruit is easy to miss. The patient should be referred to his or her family doctor within 48 to 72 hours with a photo or drawing of the retinal plaque, and an indication on the neck of the patient where the bruit was auscultated. The patient should be referred to his or her physician even if the carotid artery sounded normal, because a bruit will only occur if between 50% and 85% occlusion of the vessel is present.

Referral for Vascular Evaluation

The finding of a retinal embolism or a bruit should provide motivation for a vascular work-up. The vascular specialist will look for evidence of carotid or coronary thrombus formation. Discovery of arterial disease may prompt medical or surgical intervention.

Treatment

Left untreated, the patient with retinal arterial plaques is at extreme risk for stroke, retinal vascular occlusive disease, myocardial infarction, and kidney failure. The use of so-called "blood thinning" agents, such as aspirin, Coumadin, or heparin, may be as effective as surgical intervention at preventing target organ damage. Carotid endarterectomy is a surgical approach in which the thrombus formation of the artery is removed, thus

reducing the risk of embolism formation. Significant risks accompany this surgical approach, however, and a medical approach can be just as effective at reducing the risk of ultimate target organ damage or death of the patient.

Ocular Ischemic Syndrome

Demographics

Ocular ischemic syndrome, or OIS, has been known in the past as venous stasis retinopathy. OIS usually affects people from ages 50 to 90 years, and the mean age of involvement is 65 years. Males are affected twice as often as females and race does not appear to be a risk factor. The condition is unilateral in 80% of cases.

Symptomology

Of individuals with OIS, 90% noted a loss of vision that typically motivated them to seek out an eye examination. The decrease in vision is typically gradual and prolonged during a period of several months. An abrupt loss of vision occurs in 10% of cases, and is usually caused by a central retinal artery occlusion (CRAO) secondary to OIS. In these cases ophthalmoscopy will demonstrate a cherry red spot of the retina, and the occlusion will be the result of neovascular glaucoma causing an intraocular pressure that exceeds the perfusion pressure of the central retinal artery. Nearly half of all OIS patients complain of a dull eye ache on the involved side.

Clinical Signs

Visual acuity is reduced from 20/25 to 20/40 in a third of cases. In approximately one third of cases, visual acuity drops between 20/50 and 20/400. The remaining third of OIS patients have a dramatic reduction of VA from 20/800 to no light perception. Slit-lamp evaluation reveals flare in the anterior chamber of OIS eyes with possible rubeosis iridis. Occasional keratic precipitates may be found on the corneal endothelium. Cells may be demonstrated in the anterior chamber. Thus, any uveitis of unknown etiology in a patient 50 years or older should be evaluated for OIS. Neovascularization of the iris is seen in approximately 60% of eyes with OIS. Therefore, any rubeosis iridis in a patient 50 years or older with no history of diabetes or retinal vein occlusion should prompt a search for OIS. In the posterior pole, OIS can cause midperipheral dot and blot hemorrhages. These hemorrhages are found in 80% of eyes affected with OIS. The retinal arterial system may demonstrate microaneurysms, and approximately 30% of eyes affected with OIS have neovascularization of the optic nerve head. Central retinal artery obstruction (with the production of a cherry-red spot) with concomitant neovascularization of the iris should prompt a suspicion of OIS.

Cause of OIS

Occlusion of the carotid artery of 90% or more is necessary to cause OIS on the ipsilateral side. This reduction of homodynamic pressure within the central retinal artery reduces blood flow to ocular tissues and yields ischemia, infarction, and neovascularization.

Systemic Associations

Approximately half of all patients with OIS have been diagnosed with systemic hypertension. In addition, approximately half have been diagnosed with diabetes and approximately one third have coronary artery disease. Approximately one quarter of all patients who develop OIS have a history of cerebral stroke, and approximately 4% of OIS patients have a cerebrovascular accident (CVA) each year. Nearly 50% of patients who develop OIS die within 5 years, usually from stroke, cancer, or heart disease.

Treatment

Prompt referral for treatment is necessary, because central retinal artery occlusion has been observed after the diagnosis of OIS. Carotid endarterectomy has been shown to reverse OIS and thus reduce the risk of central retinal artery occlusion. If the carotid artery is 100% blocked, endarterectomy may not be effective because of the risk of embolism formation from the procedure. Carotid artery bypass has been shown to cause regression of OIS but has not been shown to have a long-term positive effect on visual acuity outcome. Panretinal photocoagulation to the involved retina has been shown to cause regression of the iris neovascularization but is not as effective for this purpose as when it is used in diabetic retinopathy.

CONNECTIVE TISSUE DISEASES

Connective tissue diseases, also known as collagen vascular diseases, are a group of disorders of unknown etiology that are characterized by arthritis, vasculitis, and autoimmunity. The ocular findings of these diseases are not specific, although some characteristics may help in the differential diagnosis of these diseases.

Giant Cell Arteritis

Typically a disease of the elderly, giant cell arteritis (GCA) rarely occurs in patients younger than 60 years. In this disorder, a cellular infiltration occurs of the walls of medium- to large-sized arteries throughout the body. This process produces the symptoms of neck, shoulder, and joint pain. If the superficial temporal artery of the head is involved, then fever, headaches, temporal scalp pain, and jaw claudication can result. Any elderly

patient with temporal scalp pain should have an immediate erythrocyte sedimentation rate (ESR) performed. An elevated ESR in light of these symptoms strongly suggests GCA. A temporal artery biopsy will confirm the diagnosis of GCA. The patient may experience a concurrent loss of vision resulting from posterior ciliary artery involvement, causing a classic anterior ischemic optic neuropathy (ION) of the optic nerve head, or central retinal artery occlusion (CRAO), causing a cherry-red spot. Classically, the nerve head is swollen and peripapillary hemorrhages and CWS are present on the involved side, although the retina may be minimally involved. The patient complains of a loss of vision in the involved eye. Visual field testing commonly reveals an altitudinal field defect, and external tests usually demonstrate a relative afferent pupillary defect on the involved side. Treatment of GCA should commence immediately on discovery of an elevated ESR in an elderly patient with any of the signs or symptoms described above. Once treatment is started, a temporal artery biopsy may be performed to confirm the diagnosis. Immediate treatment is the key to prevent further vascular occlusions and reduce the risk of profound loss of vision on the contralateral side, however. Treatment consists of high-dose oral prednisone (80 to 120 mg daily). Initial treatment may commence with intravenous steroids (1 gram daily for 3 to 5 days) followed by the high-dose oral steroids. Treatment is necessary for at least a year to keep the ESR and C-reactive protein normalized.

Wegener's Granulomatosis

In this disorder, a granulomatous vasculitis of the upper and lower respiratory tracts, kidneys, and other organ systems occurs. The disease can occur anytime from childhood on, and the mean patient age at onset is 40 years. It is typified by granulomas that form anywhere in the respiratory tract from the nose to the lungs. Wegener's is autoimmune in nature, with antibody and cell-mediated complexes contributing to the tissue damage. Patients usually are seen with respiratory symptoms and paranasal pain and discharge. Laboratory findings indicate kidney involvement in 85% of cases, with an elevated ESR and C-reactive protein, a positive rheumatoid factor, and an elevation of immunoglobulin G (IgG) gamma globulin. The patient will usually complain of fever and malaise. Ocular findings will be present in 50% of patients, including orbital disease with optic nerve compression yielding a loss of visual acuity, extraocular muscle palsies with resultant diplopia, and optic nerve vasculitis with disc edema, hemorrhages, and ischemia. Treatment consists of the use of cyclophosphamide (for cytotoxic treatment) to stop the disease and improve the quality of life. Corticosteroids may also be used for as long as 6 months to limit ocular tissue damage and reduce optic nerve compression to restore visual acuity.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is characterized by a derangement of the immune system that causes an exaggeration of antibody production. It is idiopathic, multisystem, and is typified by exacerbations and remissions. As many as 90% of SLE patients are women and the average age of onset is 30 years. SLE can, however, occur at any age. Although it is of unknown etiology, a genetic component definitely exists that seems to be modified by environmental influences. In fact, some drugs have been known to cause SLE. These medications include chlorpromazine, hydralazine, isoniazid, and methyldopa. The onset of the disease is heralded by the production of antibodies that react against cell constituents and have direct toxic effects on target cells. In addition, antibody-antigen immune complexes form and circulate with complement and cause a destructive inflammation to occur in the blood vessel walls. SLE causes cutaneous rashes, such as the classic butterfly malar rash across the bridge of the nose. Inflammatory arthralgias of the joints produce significant pain. Renal disease is a sequela that accounts for a portion of the mortality rate associated with SLE. Patients suspected of having SLE are given a battery of laboratory tests. The presence of four of the eleven SLE laboratory and clinical criteria identified by the American Rheumatism Association establishes the diagnosis. Lupus retinopathy typically occurs in the elderly or the very sick patient with SLE. CWS, hemorrhages, retinal edema, hard exudates, microaneurysms, and retinal vascular occlusive disease characterize this retinopathy. Cranial nerve palsies may also occur, yielding diplopia, ptosis, and a relative afferent pupillary defect. Treatment of SLE consists of nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin, antimalarial medications (hydroxychloroquine), and systemic steroids. The NSAIDs and antimalarial drugs are useful for the arthralgias and fever, and the steroids reduce the inflammation to various organ systems and control any hematological complications.

Scleroderma

A connective tissue disease of unknown etiology, scleroderma causes fibrous replacement of the skin, vascular insufficiency, and vasospasm. The primary characteristic of scleroderma is thickening of the dermis that ultimately leads to contraction and immobility of the skin. The condition starts peripherally in the fingers and toes and spreads centrally to the arms and

face. Histiologically, an increase in the concentration of collagen occurs in the skin and organ systems. Ultimately, the skin appears taut and shiny.

In addition, an increase in collagen content occurs in the walls of blood vessels. This can lead to Raynaud's disease, a condition characterized by pallor and tingling after exposure to cold, emotional stress, or vibrating tools. The patient may have difficulty swallowing, because the esophagus becomes dysfunctional, causing gastroesophageal reflux. A major cause of mortality associated with scleroderma is renal disease, leading to malignant hypertension and renal failure.

The most common ocular manifestations of scleroderma include the CWS and intraretinal hemorrhages associated with hypertensive retinopathy. The presence of optic disc edema indicates malignant hypertension caused by renal crisis. External ocular signs include tightness of the eyelids resulting in keratoconjunctivitis sicca. Rarely, extraocular muscle involvement with palsy is present. The ocular signs of scleroderma are usually associated with renal involvement, thus the presence of hypertensive retinopathy in cases of scleroderma warrants a complete renal evaluation.

The treatment of scleroderma is directed toward the associated renal crisis, and includes blood pressure control and renal dialysis. Calcium channel antagonists are useful to control the symptoms of Raynaud's phenomenon. The systemic sclerosis is difficult to control, although the use of D-penicillamine is of some benefit. Survival rates are improved by using this agent. Systemic steroids have not been shown to be effective in the treatment of scleroderma.

Rheumatoid Arthritis

Prevalence in the population of as much as 2.0% makes rheumatoid arthritis (RA) the most common of all collagen-vascular diseases. RA is characterized by an insidious onset of a symmetrical, deforming polyarthritis, mostly of the hands and feet. The bones at the joints become eroded with eventual destruction. RA is characterized by morning stiffness, arthritis of at least three joints simultaneously and symmetrically, and a positive rheumatoid factor (RF). Radiology helps to confirm the diagnosis.

The ocular involvement in cases of RA includes keratoconjunctivitis sicca, Sjögren's syndrome, episcleritis, and scleritis. The scleritis may be anterior, posterior, or necrotizing. Scleritis occurs in 1.0% of patients with RA. In patients with scleritis, as many as one third have RA. The cornea in RA patients may exhibit a benign or necrotizing marginal furrow.

Posterior segment involvement is rare, although in some cases of RA CWS have been noted and are responsive to oral corticosteroids.

Treatment of RA includes the antimalarial medications chloroquine and hydroxychloroquine, which display antiinflammatory effects. Usually, treatment begins with nonsteroidal antiinflammatory drugs (e.g., aspirin, indomethacin, and naproxen), proceeds to slow-acting antirheumatic drugs (e.g., gold, hydroxychloroquine, and D-penicillamine), low-dose prednisone, and finally, methotrexate. RA-associated anterior scleritis is treated with indomethacin, and posterior scleritis is treated with systemic corticosteroids.

The treatment of RA patients with the antimalarial drugs chloroquine or hydroxychloroquine mandates a posterior evaluation twice yearly to monitor for the formation of a "bull's-eye" pigmented retinopathy. This maculopathy is caused by an accumulation of these antimalarial drugs in the macula and is considered a potentially harmful sequela of toxicity to the medications. The biannual exam should evaluate for any reduction in visual acuity, any visual field loss by using a macula test with red stimulus, color vision changes, Amsler grid changes, and funduscopy. Early detection of a pigmentary maculopathy can lead to a reversal of the condition on discontinuation of the medication, but if ocular toxicity is detected late it may be irreversible and cause permanent visual changes.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a multisystem, necrotizing inflammatory disease that causes a vasculitis of the small- and medium-sized arteries. PAN is characterized by the deposition of immune complexes in the walls of the blood vessels, particularly at the sites of branching and bifurcation. Mean patient age at onset is 45 years, and males are 2.5 times more likely to be affected than females. All layers of the vessel wall demonstrate polymorphonuclear leukocytic infiltration that result in edema and necrosis. As the vessel wall thins and weakens, an aneurysm develops that can rupture and cause tissue necrosis. Vascular occlusion can also result from the deposition of immune complexes in the anterior wall.

PAN most often affects the heart, kidneys, liver, gastrointestinal (GI) tract, CNS, and skin. At first the clinical symptoms include fever, weight loss, malaise, headache and abdominal pain. PAN can result in renal and heart failure and arthritis. Laboratory tests demonstrate leukocytosis and an elevated ESR.

Of PAN patients, 10% demonstrate ocular manifestations of the disease. In some cases, the earliest sign of PAN is exophthalmos and orbital pseudotumor. A PAN-associated scleritis may lead to a retinal detachment. The most common ocular finding in PAN is choroidal vasculitis. When the retinal vessels become involved, a resultant retinopathy is produced that is characterized by edema, vasculitis, CWS, hemorrhages,

and exudates. Ultimately, retinal vascular occlusions can occur that lead to neovascularization. Choroidal vascular involvement can cause TIAs, ION, disc edema, and optic nerve head hemorrhages.

PAN can be fatal, usually caused by kidney disease, myocardial infarction, congestive heart failure, liver failure, bowel perforation, or CVA. Treatment of PAN with oral steroids may yield symptomatic relief and increase survival rates. Combining steroids with immunosuppressive agents has dramatically improved the prognosis of the disease.

SARCOIDOSIS

This multisystem, granulomatous disease of unknown etiology is considered an inflammatory condition because no known etiologic factor has been isolated. It is thought that airborne antigens are inhaled and stimulate a granulomatous response in the lungs. Antigens then spread through the bloodstream to all organ systems, including the eye, and can cause a wide range of inflammatory responses. Almost one third of all ocular sarcoidosis involves the posterior segment. Typically, a disseminated chorioretinitis will be present (Figure 22-1), and in active conditions an accompanying overlying vitritis will occur. Pathognomonic of ocular sarcoidosis is a periphlebitis caused by an infiltration of white blood cells in the walls of the retinal vessels. This takes on the appearance of the classic "candle-wax drippings," causing the vessel to be encased in a white sheath (Figure 22-2). Other posterior manifestations of sarcoidosis include "snowballs" along the pars plana, retinal neovascularization, and vitreous hemorrhages (Figure 22-3). Cream-colored nodules indicative of sarcoid granulomas may invade the retina and optic nerve. Disc edema may occur in cases of nodular invasion of a single optic nerve, and papilledema may result from granulomatous deposition within both nerves of the brain.

INFECTIOUS DISEASES

Bacterial Infections

Tuberculosis

Caused by the acid-fast bacterium *Mycobacterium tuberculosis*, tuberculosis (TB) cases are increasing because of by the rise of HIV-infected individuals, who act as a reservoir for infectious diseases. TB most commonly affects the pulmonary system, although any organ system may become involved. The initial infection can cause a fever with coughing and upper respiratory symptoms. Reinfection leads to devastating episodes of night sweats, recurrent fevers, weight loss, and photophobia.

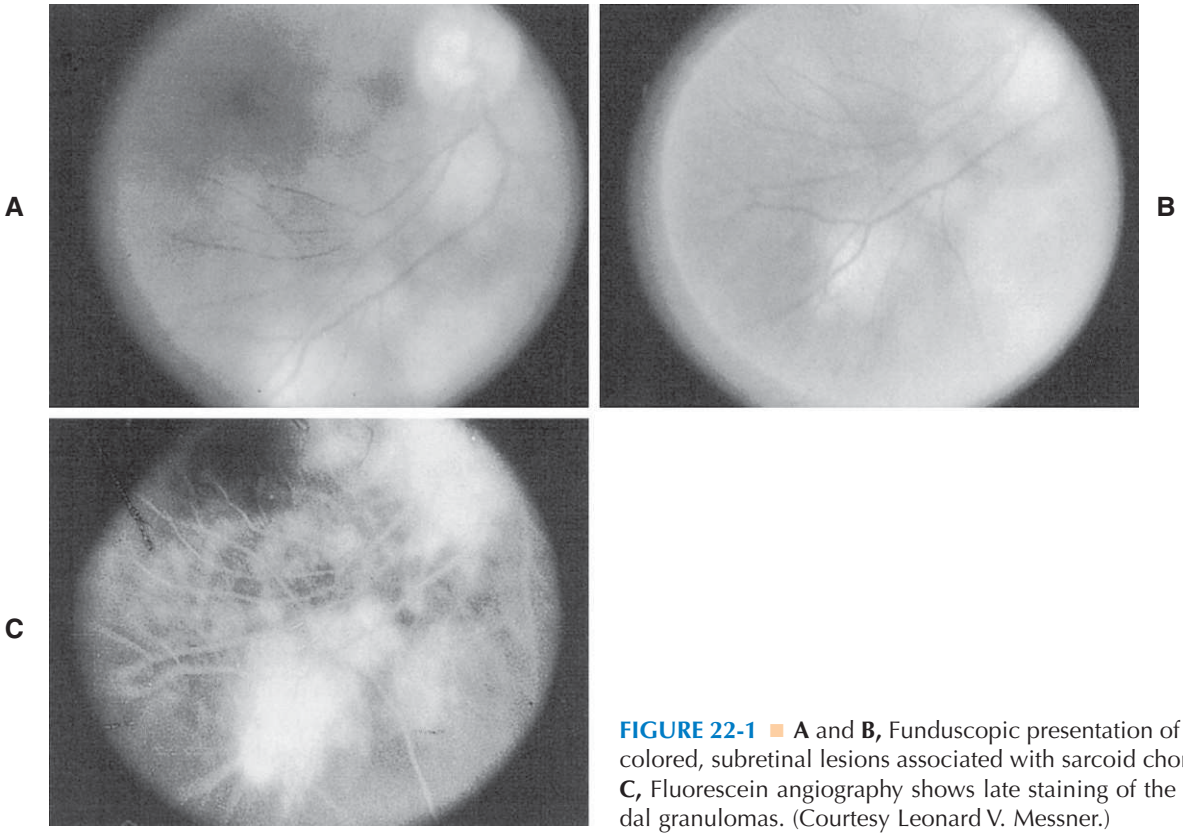

FIGURE 22-1 ■ **A** and **B,** Funduscopic presentation of cream-colored, subretinal lesions associated with sarcoid choroiditis. **C,** Fluorescein angiography shows late staining of the choroidal granulomas. (Courtesy Leonard V. Messner.)

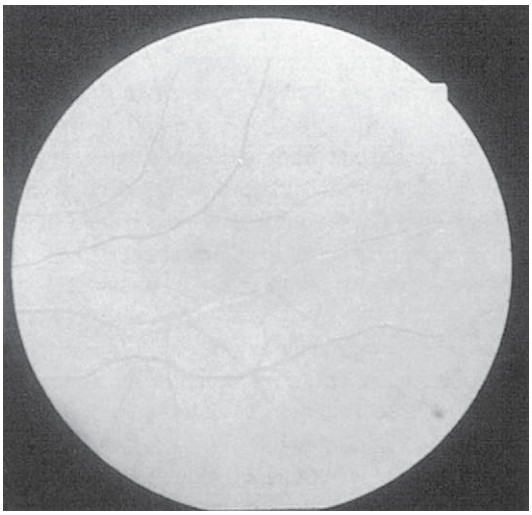

FIGURE 22-2 ■ A sheathed retinal vessel in a case of ocular sarcoidosis taking on the appearance of "candle-wax drippings." (Courtesy Leonard V. Messner.)

TB can cause a chronic granulomatous uveitis with vitreous opacities, vitritis, choroiditis (with yellow choroidal lesions), and infectious optic neuropathy. The optic neuropathy consists of tuberculoma lesions of the meninges, optic nerves, or optic nerve head. Laboratory tests include a chest x-ray, Mantoux test (injection of denatured TB bacteria) as part of a PPD (purified protein derivative) anergy panel, and sputum cultures.

Once the diagnosis is confirmed, treatment consists of pyrazinamide, rifampin, and isoniazid daily for 2 months, and rifampin and isoniazid for 4 additional months. Ethambutol may also be used in conjunction with this treatment. Corticosteroids and vitamin B_6 supplements may be part of the therapeutic regimen.

Syphilis

Treponema pallidum is a highly infectious spirochete that is spread by sexual contact. In the primary disease, formation of a painless chancre occurs, usually at the site of infection. When the disease progresses to its secondary stage, the patient experiences flu-like symptoms and, possibly, photophobia from uveitis. In its tertiary stage, cardiac involvement may occur with neurologic changes caused by spread of the spirochete to the cerebrospinal fluid.

In congenital syphilis, a resultant salt-and-pepper fundus can be caused by RPE inflammation and optic atrophy. Acquired syphilitic retinopathy includes posterior scleritis, retinal vascular occlusions, retinitis, and cystoid macular edema (Figure 22-4).

Laboratory tests for syphilis include the fluorescent treponemal antibody absorption (FTA-ABS) or microhemagglutination (MHA-TP), and the rapid plasma reagin (RPR), or venereal disease research laboratory (VDRL). The treatment of syphilis includes the use of penicillin or, if allergy is an issue, then doxycycline or erythromycin.

Lyme Disease

Like syphilis, Lyme disease is caused by a spirochetic infection by *Borrelia burgdorferi,* and is usually transmitted by the bite of an infected Ixodes tick. The ticks feed on the white-footed mouse and the white-tailed deer, and these, as well as other animals, act as reservoirs for the spirochetes. The ticks are disseminated through much of the world by migratory birds.

Like syphilis, untreated Lyme disease has three stages. In the earliest stage the patient may have a skin rash and flu-like symptoms for as long as a month after the bite. In stage two, there may be multiple skin lesions, joint pain, uveitis, pericarditis, and a stiff neck for 1 to 6 months after the bite. In the third stage, 6 months to years after the bite, the disease becomes chronic. The spirochete infection involves the knee joints, causing pain, and the CNS, causing memory loss, dementia, and multiple sclerosis (MS)–like symptoms.

Posterior involvement most often is seen as a pars planitis (intermediate uveitis), characterized by "snowballs" along the pars plana, and an associated vitritis.

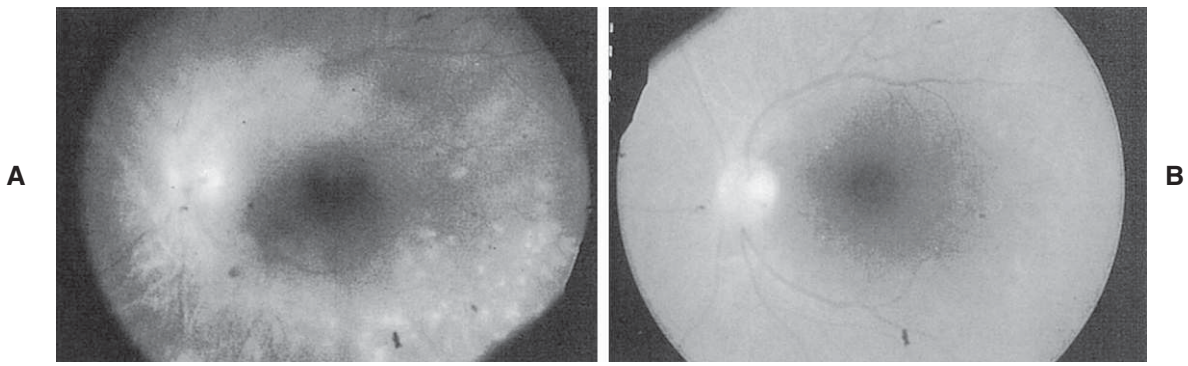

FIGURE 22-3 ■ **A,** Disseminated, white retinitic foci with vitritis and vitreous hemorrhage. **B,** The same patient after a 6-week treatment regimen of oral prednisone. Note the regression of the inflammatory process and vitreous hemorrhage. (Courtesy Leonard V. Messner.)

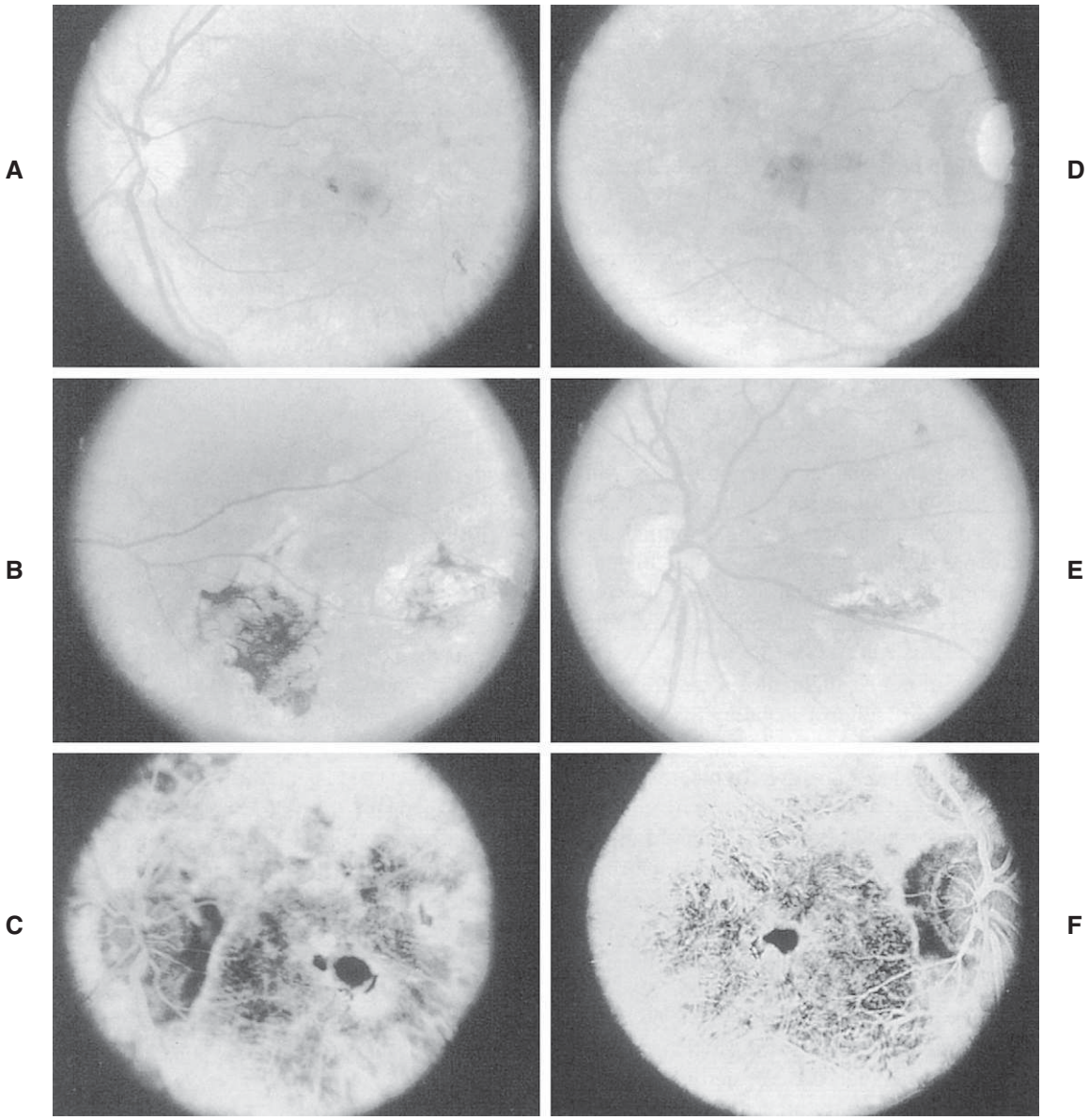

FIGURE 22-4 ■ Bilateral syphilitic chorioretinitis. The left (**A** and **B**) and right (**D** and **E**) fundi exhibit disseminated chorioretinitic lesions with chorioretinal scarring and pigmentary hyperplasia. Fluorescein angiography (**C** and **F**) shows extensive disruption of the retinal pigmentary epithelium, depicted as generalized, hyperfluorescent window defects. (Courtesy Leonard V. Messner.)

The retina may demonstrate vasculitis, macular edema, and exudative retinal detachments. Both optic nerves may swell, causing papilledema secondary to Lyme meningitis. Pseudotumor cerebri (PTC), optic neuritis, and ION have all been associated with Lyme disease. Ultimately optic atrophy may result from Lyme disease involving the CNS.

Lyme disease may be diagnosed early by the formation of a skin rash in a patient with typical symptoms who is living in an endemic area. Nonetheless, the early diagnosis can be problematic, since the patient rarely realizes that a tick bit her, and the rash is seen in only one third to two thirds of cases. Laboratory testing includes enzyme-linked immunosorbent assay (ELISA) testing and a confirmatory Western blot test, but is often unreliable and insensitive.

Treatment is often started on a patient who either was bitten by a tick and demonstrates a typical postbite, silver dollar–sized red rash, or who has no rash or bite history but has typical symptoms and lives in an endemic area. Oral doxycycline, amoxicillin, or azithromycin has been found to be effective in stage one of the disease. In the more advanced stages of Lyme disease, intravenous antibiotics are often required.

Fungal Infections

Histoplasmosis

Inhalation of the yeast fungus *Histoplasma capsulatum* causes initial infection of the lungs. The fungus can then travel to all organ systems of the body. The fungus most often is found in soil near bird and bat droppings and the most common patients infected live along the Mississippi valley from Ohio to Alabama and Texas.

Histoplasmosis (POHS) causes a classic triad of retinal findings: macular subretinal neovascularization (SRNVM), peripapillary atrophy, and peripheral choroidal "punched-out" atrophic lesions. This triad results in a disciform macular scar with possible metamorphopsia or central scotoma, and a possible retinal detachment. Ultimately, optic disc edema may occur.

The fundus findings indicate the diagnosis, and laboratory tests are usually not needed. Bilateral fluorescein angiography (FA) should be performed to detect and evaluate subretinal neovascularization. Treatment includes verteporfin photodynamic therapy of the SRNVMs.

Mucormycosis

A rare fungal infection that most often occurs in the elderly or the immunocompromised, mucormycosis is most commonly seen in patients in ketoacidosis from diabetes. It is a devastating disease with a morbidity rate as high as 90%. It has been seen in young, diabetic drug-abusers who inhale cocaine, thus introducing the fungus into their nasal mucosa. The fungal infection quickly enters the bloodstream and travels to the brain, causing a cavernous sinus syndrome (CSS). In cases of CSS secondary to mucor infection, the patient may experience diplopia, orbital pain, photophobia, and ptosis. The pupil on the involved side can become dilated, and the conjunctiva becomes engorged. The retina vessels exhibit "box-carring," or segmentation of the column of blood in the lumen caused by venous stasis.

Treatment includes the antifungal agent amphotericin B with surgical debridement of the necrotic tissue, but the prognosis for survival remains very poor.

Viral Infections

Herpes Simplex Virus I

A DNA virus, herpes simplex virus 1 (HSV-1) is transmitted by direct contact in children and adults. HSV-1 rarely causes genital lesions, and the primary infection may be mild and go unnoticed. The virus then remains dormant in the nerve ganglia until stress, trauma, or sunburn causes a reactivation of the virus. The virus then travels to the dermatome of the involved nerve and causes a cold sore or an associated proliferation of skin vesicles.

The diagnosis of HSV-1 is usually made on the basis of the patient's signs, symptoms, and history. The Tzanck cell test of skin scrapings can confirm the diagnosis

Posterior ocular involvement includes endophthalmitis and chorioretinitis. HSV-1 infection may lead to an acute retinal necrosis composed of vasculitis, retinal hemorrhages, and retinal necrosis. In addition, HSV-1-associated encephalitis, although uncommon, may cause retinal hemorrhages, retinitis, vasculitis, and exudative retinal detachment. The treatment of the posterior involvement of HSV-1 is aimed at improving the prognosis of the associated encephalitis. Adenosine arabinoside (ARA-A) and acyclovir decrease the mortality rate associated with HSV-1-associated encephalitis. The treatment of the acute retinal necrosis remains problematic, however.

Herpes Simplex Virus 2

A DNA virus, herpes simplex virus 2 (HSV-2) is transmitted by direct sexual contact, and genital-ocular transmission can occur. Neonatal infection can occur by the infant's passage through the birth canal and contact with infected maternal fluids. HSV-2 is characterized by recurrent and painful genital ulcers.

Posterior segment involvement occurs in one fifth of encephalitis cases and includes a retinitis with hemorrhages, CWS, vasculitis, retinal detachment, and optic neuritis.

Treatment of HSV-2 encephalitis-related retinitis by using intravenous acyclovir has been shown to be effective, but a risk of serious side effects exists in neonates.

Herpes Zoster Virus

The primary infection of herpes zoster (HZV) causes chickenpox, a highly contagious disease mostly found in infants and children. After the initial clinical manifestations of a mild, vesicular body-wide rash and a week of mild fever, malaise, and headache, the child usually recovers. Sometimes no other signs or symptoms are present but the rash.

During this infection, the varicella (or chickenpox) virus gains access to the sensory ganglion, where it lies dormant. Reactivation of the virus later in life occurs caused by, among other factors, emotional or physical stress, age, or a compromised immune system. The virus travels along the nerves to the skin and produces painful vesicular eruptions. The area of skin served by the infected nerve or nerves first begins to tingle, and the patient may have a fever and headache. Next, the eruption of vesicles that follows this prodrome can be exquisitely painful and is known as shingles. The blisters eventually scab and complete resolution occurs in approximately 4 to 6 weeks. The patient may be left with postherpetic neuralgia (PHN), a persistent, intense, boring pain around the involved eye.

Very rarely acute retinal necrosis (ARN) occurs, and, in addition, vascular occlusive diseases, optic neuritis, and multifocal choroiditis.

Oral antiviral agents, including acyclovir, famciclovir, or valacyclovir, are mandatory in the treatment of HZO patients within 2 to 3 days of the onset of rash, and should be continued for 7 days. This treatment has been shown to reduce the risk of PHN and it can be effective against ARN secondary to HSV. In patients 40 years or younger, any case of HZO should inspire a diligent search for immunosuppression caused by HIV infection.

Rubeola

This RNA virus causes measles with a mild fever and rash. Rubeola is highly contagious and usually occurs in childhood. In rare cases, rubeola may cause severe bilateral neuroretinitis. This condition occurs a week after the rash appears, and causes dramatic vision loss. Funduscopy reveals diffuse optic disc and macular edema, venous dilation and subsequent optic atrophy. Visual fields will be constricted and permanent visual acuity loss occurs. No treatment exists for the retinopathy.

Rubella

Rubella is the virus that causes German measles, and is common and very contagious. Rubella causes a mild infection in children and adults. The virus is spread by direct contact, and symptoms are a mild fever, lymphadenopathy, and a rash.

Immunization programs in the United States have made congenital rubella rare, but 20% of U.S. women are still susceptible to infection. If rubella occurs in the first trimester of pregnancy, the results can be devastating to the fetus. Of children infected in the first trimester, 80% will develop one of the signs of congenital rubella, either at birth or later in life.

The most common manifestation of congenital rubella is hearing loss, and heart disease develops in two thirds of patients. Other stigmata include mental retardation, microcephaly, vascular effects, and ocular disease.

Almost half of all children with evidence of congenital rubella have the ocular complications of corneal clouding, cataract, glaucoma, strabismus, nystagmus, microphthalmos, or posterior segment disorders. The retinopathy of congenital rubella consists of a salt-and-pepper fundus and a loss of the foveal reflex. The pigmentary changes are stippled and are at a uniform depth under the retinal vessels. Interestingly, the visual acuity is rarely affected and the visual field is typically normal when only the retina is involved. Visual acuity can be significantly reduced, however, by the presence of a choroidal neovascular membrane.

No treatment exists for the retinopathy, and the choroidal neovascular membrane appears later in life and involves the center of the foveal zone. Thus, it is usually not amenable to laser therapy.

Epstein-Barr Virus

A ubiquitous virus that has infected most adults and is the cause of mononucleosis, Epstein-Barr virus (EBV) is confirmed by serological testing in patients with the typical symptom of extreme lethargy.

EBV has been implicated as the cause of a multifocal choroiditis with panuveitis. In this case patients may experience a visual acuity drop to light perception and the funduscopic evaluation reveals yellow-gray RPE lesions with shallow serous detachment over the active lesions. A relative afferent pupillary defect (RAPD) may be present and associated with a mild papillitis.

The treatment for EBV includes acyclovir and laser therapy for choroidal neovascularization. All children and adults with mononucleosis should have a dilated fundus evaluation to monitor for active retinal lesions and neovascularization.

Cytomegalovirus

Although cytomegalovirus (CMV) may affect the brain, lungs, GI tract, liver, and spleen, the most frequent manifestation is in the eyes. This DNA virus is a member of the herpes family of viruses and is transmitted by contact with bodily secretions. CMV retinopathy may occur when the immune system is compromised, as in AIDS, and when the CD4 count, which monitors the status of the immune system, is less than 50 cells/mm^3.

CMV retinopathy is usually asymptomatic and is discovered on routine eye examination. If the posterior pole is involved, however, the visual acuity may be affected and scotomata may develop. CMV retinopathy consists of retinal hemorrhages and CWS with exudates that take on the classic appearance of a "cheese and ketchup" fundus (Figure 22-5). An associated necrotizing retinitis (Figure 22-6), and vascular sheathing with rhegmatogenous retinal detachment may be present. Cystoid macular edema, papillitis, and cataract development may be present.

CMV retinitis is the leading cause of blindness in the AIDS population. Therapy for CMV retinitis consists of intravenous antiviral agents (ganciclovir, foscarnet, and cidofovir), intraocular injection of ganciclovir (Vitrasert), and intravitreal injection of antiviral agents.

Regression of CMV retinopathy usually occurs in less than a month, but antiviral therapy must be maintained for the life of the patient. Therapy for CMV retinopathy may be discontinued, however, if the pa-

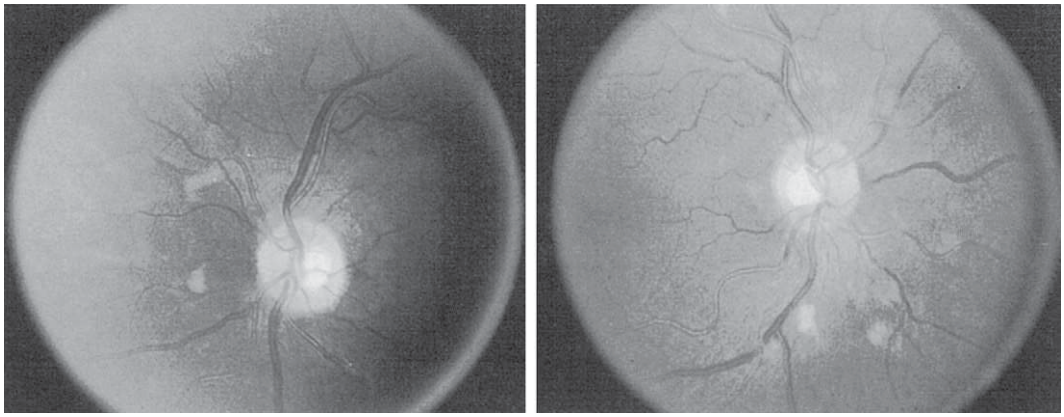

FIGURE 22-5 ■ Cotton-wool spots surrounding the left **(A)** and the right **(B)** optic discs in a patient with AIDS. Nerve-fiber layer infarcts represent the most common presentation of noninfectious retinal microangiopathy associated with AIDS. (Courtesy Leonard V. Messner.)

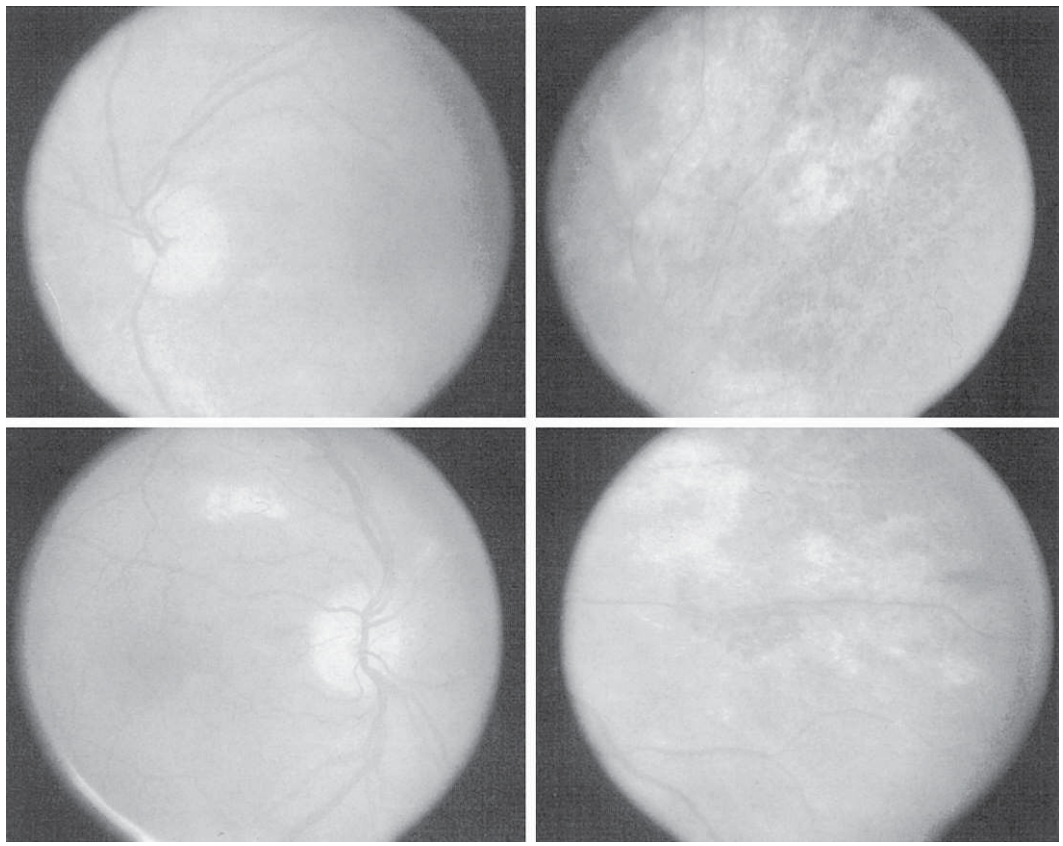

FIGURE 22-6 ■ CMV retinitis in a patient with AIDS. **A,** Localized areas of retinitis are seen above and below the left optic disc. **B,** The midperipheral eyegrounds of the left eye reveal confluent areas of necrotizing retinitis with intraretinal hemorrhage and pigmentary mottling. **C,** In the right eye, patchy areas of retinitis are evident along the superotemporal arcade and superonasal to the optic disc. **D,** Confluent retinitis with intraretinal hemorrhage, pigmentary disruption, and sheathed vessels can be observed nasal to the right optic nerve head. Note the presence of "satellite" lesions along the peripheral border of confluent retinitis, representing areas of active viral replication. (Courtesy Leonard V. Messner.)

tient's cluster of differentiation 4 (CD4) count remains above 100 to 150 cells/mm^3 for 3 to 6 months while on therapy.

If a CWS is found on funduscopy in an asymptomatic patient with no significant medical history, then a CD4 count and serological testing is warranted to confirm the presence of an HIV infection.

CMV retinopathy must be differentiated from noninfectious HIV retinopathy, which typically reveals nonprogressive CWS. No treatment is needed in cases of HIV retinopathy. Differentiation is determined by progression: if the CWS worsen and become associated with hemorrhages, then CMV retinopathy is most likely the etiology. A nonprogressive CWS in an HIV patient is most likely caused by noninfectious HIV retinopathy.

Parasitic Infections

Toxoplasmosis

Caused by the intracellular protozoan parasite *Toxoplasma gondii,* toxoplasmosis is spread by the eating of uncooked meat. These cases may be reactivations of congenitally transmitted toxoplasmosis from the mother to the fetus. Toxoplasmosis typically affects the retina and nervous system. It causes a yellow-white lesion of the posterior pole, and in active cases an overlying vitritis will be present. An associated disc edema, vitritis (Figures 22-7 and 22-8), subretinal fibrosis and lipids (Figure 22-9), vascular-occlusive disease, and lymphadenopathy may be present.

One in every 3000 births in the United States results in a case of congenital toxoplasmosis, with half of these babies born healthy and exhibiting no clinical signs of the disease. Laboratory tests include a serum antitoxoplasma antibody titer and an anergy panel.

Large, exudative retinal lesions near the macula require treatment with sulfadiazine with clindamycin and prednisone. Pyrimethamine (Daraprim), a folate antagonist, has also been prescribed for toxoplasmosis in conjunction with folinic acid (to reverse a low platelet count).

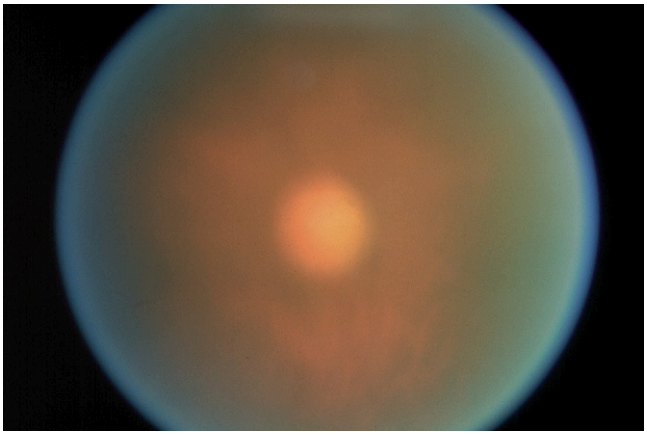

FIGURE 22-7 ■ A juxtapapillary retinitis with severe overlying vitritis in an 8-year-old boy who is seropositive for *Toxoplasma gondii.*

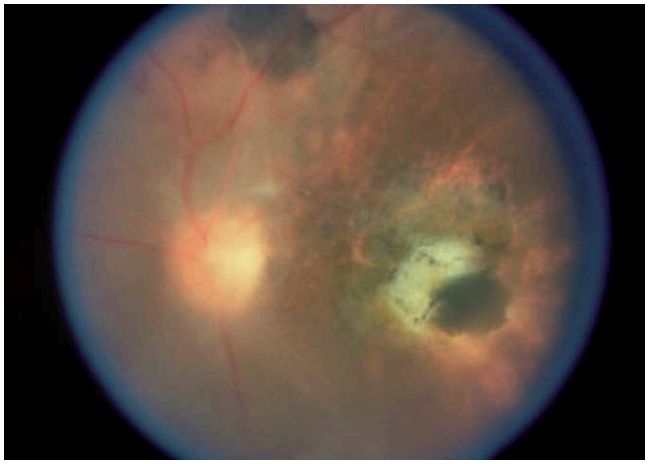

FIGURE 22-8 ■ Reactivation of *Toxoplasma* retinochoroiditis. Active retinitis can be appreciated as a fluffy white area that is contiguous with a pigmented, previously active chorioretinitic lesion. Inflammatory cells are evident in the vitritis overlying the area of active inflammation.

Toxocariasis

An infection caused by larvae of the *Toxocara canis* roundworm, toxocariasis is found typically in young children who ingest animal feces (mostly from puppies) that contain the worm eggs. The eggs hatch in the intestines and the worm larvae enter the systemic circulation, spreading to the vital organs and eyes.

In infected children an associated fever, cough, skin rash, abdominal pain, and visual impairment may be present. In the eyes, toxocariasis can cause a peripheral chorioretinal granuloma (Figure 22-10), a posterior pole chorioretinal granuloma near the macula (Figure 22-11), or endophthalmitis.

No proven treatment exists for toxocariasis, and the disease tends to be self-limiting. Various antihelminthic medications have been recommended, but these are still of unknown benefit.

HEMATOLOGICAL MANIFESTATIONS

Platelet Abnormalities

Because platelets allow for hemostasis by forming vascular plugs at sites of vessel disruptions, coagulative disorders may result in significant fundus abnormalities.

Thrombocytopenia

Accelerated platelet destruction in idiopathic thrombocytopenic purpura (ITP) or drug exposure can both cause a reduction in the total number of platelets, a condition known as thrombocytopenia. The retinal

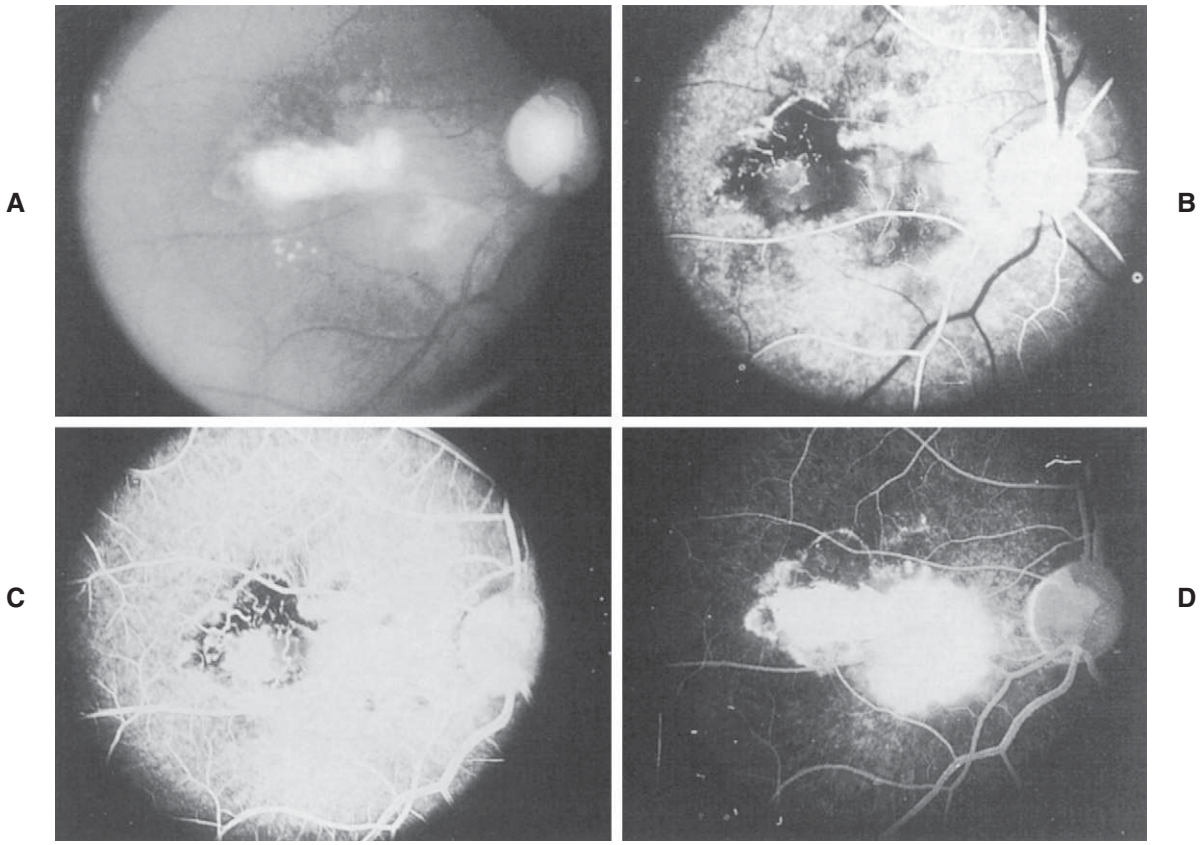

FIGURE 22-9 ■ **A,** An inactive, macular toxoplasmotic lesion with associated subretinal fibrosis and lipid. **B** to **D,** Fluorescein angiography reveals a subfoveal choroidal neovascular membrane that progressively fills with fluorescein and shows profound leakage late in the angiogram. (Courtesy Leonard V. Messner.)

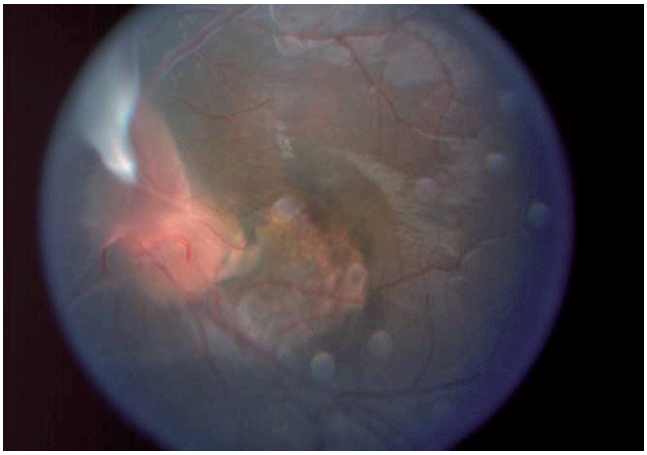

FIGURE 22-10 ■ Peripheral *Toxocara* inflammatory lesion with extensive transvitreal fibrosis communicating with the optic nerve. The optic disc and macula have been dragged toward the superonasal quadrant. Linear retinal breaks are evident adjacent to and below the fibrous vitreal membrane.

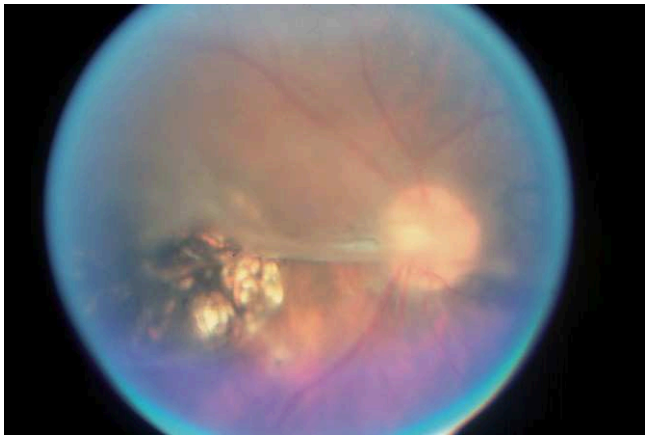

FIGURE 22-11 ■ A focal toxocaral granuloma with fibrous traction band extending into the optic nerve head.

findings in this condition include vitreous and retinal hemorrhages with bilateral serous retinal detachments and disc edema.

Thrombotic thrombocytopenic purpura (TTP), a disease associated with anemia, fever, CNS dysfunction, and renal disease, can result in papilledema with retinal hemorrhages and serous detachments secondary to retinal pigmentary epithelial (RPE) damage and focal occlusions of the choriocapillaris.

Drug-induced thrombocytopenia can also significantly affect the retina. For example, the use of aspirin in a patient with age-related macular degeneration may predispose a choroidal neovascular membrane to

bleed. This can result in massive subretinal and vitreous hemorrhaging and lead to vision loss. Interestingly, studies have shown that aspirin does not affect the progression of diabetic retinopathy.

White Blood Cell Abnormalities

Leukemia

An elevation in the white blood cell count (WBC) can lead to leukemic infiltration of the choroid, retina, or vitreous. Funduscopic evaluation reveals multifocal retinal pigment epithelial defects and serous detachments of the RPE and retina. Leukemic retinopathy consists of vitreous and posterior pole retinal hemorrhages with CWS. Venous occlusion and retinal neovascularization may occur caused by the hyperviscosity caused by leukemia. The retinopathy is treated indirectly by appropriately treating the underlying hematological disorder.

Red Blood Cell Abnormalities

Anemia

A reduced red blood cell count (RBC) may lead to anemic retinopathy consisting of retinal hemorrhages, edema, exudates and disc edema.

Polycythemia

An elevation of the RBC above six million may produce marked dilation and tortuosity of the retinal vessels that leads to venous stasis retinopathy. Characteristically, superficial and deep intraretinal hemorrhages and disc edema are present.

Sickle Cell Anemia

This hemoglobinopathy produces the worst retinal abnormalities in patients who inherit the sickle cell hemoglobin SC (double heterozygous genotype) gene. In this disease, the red blood cell exhibits resistance to malaria. The sickle-type hemoglobin causes deformation of the erythrocyte under conditions of decreased oxygen tension, however. The abnormally shaped red blood cells become trapped in capillaries, causing occlusions. This produces hypoxic conditions to the organs with low-pressure hemodynamics, including the lungs, GI tract, spleen, and bone. In the eye, sickle cell anemia (SCA) may produce nonproliferative retinal lesions (vascular tortuosity, retinal hemorrhages, and black sunburst lesions), or proliferative changes. Proliferative SCA evolves through five stages, beginning with peripheral arteriolar occlusions (stage I) and leading to peripheral arteriovenous (AV) anastomoses (stage II), "sea-fan" neovascularization (stage III), vitreous hemorrhage (stage IV), and, finally, retinal detachment (stage V). Laser photocoagulation can be applied in a panretinal photocoagulation (PRP)–like pattern for treatment of the neovascular tissue.

RETINAL/CHOROIDAL TOXICITY

Talc Retinopathy

This toxic retinopathy occurs in patients who are substance abusers and inject drugs such as methylphenidate (Ritalin) that are diluted, or "cut," with talcum powder. The talc particles deposit in the retinal capillaries outside the foveal avascular zone or inner retinal tissues of the macula. The talc particles appear as glistening white shining dots within a retinal vessel. They can simulate carotid emboli, but in the case of talc retinopathy dozens of particles are usually present in both fundi, whereas carotid are typically (but not always) few in number and unilateral. No treatment is needed because these particles are typically benign and cause no symptoms, but CWS and exudates have been known to occur caused by vascular occlusion. Proliferative disease secondary to talc retinopathy is very rare and is amenable to laser photocoagulation therapy.

Phenothiazine Retinopathy

Thioridazine (Mellaril) and chlorpromazine (Thorazine) are the phenothiazines that most commonly cause pigmentary retinopathy. Patients who take any phenothiazine medication should be evaluated for retinopathy at least once yearly with visual acuities, color testing, funduscopic evaluation, and visual fields to ensure that retinal pigmentary changes are not occurring. The prescribing physician should be made aware when pigmentary retinopathy is discovered. By changing the medication, the physician will be able to avoid further toxic effects while continuing to appropriately manage the mental health of the patient.

Chloroquine Retinopathy

These medications are used in the treatment of RA and SLE, and can cause a "bull's-eye" maculopathy. This condition is caused by a mottling of the RPE in the fovea and parafoveal areas. Hydroxychloroquine is less likely to cause a retinopathy than chloroquine. It is suggested that patients on these medications be tested twice yearly with red stimulus visual field testing, Amsler grid testing, visual acuities, fundus evaluation, and photographs. Any macular granularity or loss of the foveal reflex while taking either of these medications should warrant concern of a potential retinal toxic reaction.

Tamoxifen Retinopathy

Some forms of breast cancer are stimulated to proliferate by the attachment of estrogen molecules to estrogen receptors in the cytoplasm of cells. Tamoxifen is an antiestrogen medication that attaches to these receptor sites, thus competing with estrogen. By competing

with estrogen, tamoxifen has been shown to reduce the rate or reoccurrence of breast cancer. The medication has been shown to be toxic to the retina, even in small doses. The retinopathy is usually discovered on routine examination, although there may be a blurring of vision that motivates the patient to seek an eye examination. Multiple refractile particles are deposited in the macula, with the superficial deposits being white and the deeper lesions yellow. Cystoid macular edema (CME) can result in reduced visual acuities. Titration of the medication may be necessary to reduce the retinopathy and prevent maculopathy, but the risk of recurrent metastatic breast cancer must be weighed against the benefit of stabilization or reversal of the retinopathy.

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CHAPTER 23

Genetics and Oculosystemic Disease

CHAPTER OUTLINE

Despite the recent and dramatic proliferation of new insights into the genetic basis of disease, the integration of genetics into optometric practice remains a daunting task. To this end, Charles M. Wormington, Ph.D., O.D., has promoted the concept of "molecular optometry," whereby eye care practitioners are sensitized to the genetic basis of oculosystemic disease. This approach involves an understanding of the basics of genetics, an appreciation for the new discoveries in the field of genomics, and a practical means for implementing the "new genetic" thinking into the practice of optometry.

BASIC GENETICS

The Human Genome

All the information necessary for the production and maintenance of human life is found stored in the human genome. The human genome is made up of 23 different chromosomes.

Genes

Approximately 50,000 genes are contained in these 23 chromosomes. A single gene is a code for a certain product, and genes are a way to pass traits from one generation to the next.

DNA

Each gene is composed of deoxyribonucleic acid (DNA). DNA is a double-stranded helix composed of four bases: adenine (A), guanine (G), thymidine (T), and cytosine (C). A is always paired to T, and G is always paired to C. DNA is responsible for the transmission of genetic information and is particularly stable, can be faithfully replicated, and has fantastic diversity because of pairing of its bases. For example, in areas of the gene that code for proteins, DNA bases are arranged in triplets, called codons, in which a single codon specifies a certain amino acid.

Base Pairs

Three billion base pairs compose the DNA found in a single genome. All cells within a single human body contain the same 3 billion base pairs. All genes are made of DNA, but only approximately 10% of the DNA in a genome encodes genes. The remaining DNA is repetitive and its function is not well understood.

RNA

Information that is encoded in the DNA mostly concerns the production of specific proteins, although it may also consist of ribonucleic acid (RNA). Information is transmitted from DNA to RNA for the eventual production of a protein. A special type of RNA, messenger RNA (mRNA), is encoded by a certain "sense strand" of the DNA double helix and is translated into proteins.

Transcription

mRNA is created by genes through a process called transcription. mRNA is then used to express the information encoded in the DNA, usually for the production of a specific protein.

Translation

The mRNA produced by transcription is then used to produce the desired protein in a process called translation. The protein consists of a specific amino acid sequence. Only approximately 2% of the human genome is used to produce proteins, and some of the rest controls the expression of genetic information and the coding of some RNA molecules. The majority of the human genome has an unknown function, however.

The Human Genome Project

The human genome project (HGP) began in the mid 1980s and succeeded in characterizing the entire human genome. The result is the sequencing of the entire DNA of the human being. The genetic map produced revealed that all human disease has a genetic component. Practically all biomedical research is now centered on genetics and the study of complex genetic disease.

Mutations

When a change in the primary nucleotide sequence of DNA occurs, the result is called a mutation. Mutations represent a fundamental change in the product produced by the affected gene, and so may be lethal, deleterious, or advantageous to the organism. A mutation occurring in the sperm or egg (the germline) produces changes that are transmitted to the progeny.

Chromosomal Disorders

The presence of more or less than the 22 pairs of autosomal chromosomes and one pair of sex chromosomes has dramatic and deleterious effects on the human organism. The results are known as chromosomal disorders and they are the most common cause of fetal loss and the presence of birth defects in surviving progeny.

Mitochondrial Defects

Defects in the mitochondria produce metabolic and neurodegenerative disease. The eye is particularly vulnerable to mitochondrial disorders. Chronic external ophthalmoplegia (CPEO) is caused by single deletions in mitochondrial DNA and is characterized by ptosis, ophthalmoplegia, and myopathy of the limbs.

Leber's hereditary optic neuropathy (LHON) is a chronic, painless, bilateral vision loss that usually occurs in males in their late teens and early 20s. The vision loss is caused by mDNA mutations and tobacco and alcohol use.

FUNCTIONAL GENOMICS

Although the study of the patterns of inheritance of specific traits is well known as "genetics," the study of the function of genes and genomes is known as "genomics." According to Jameson and Kopp, understanding gene regulation and function can provide a better insight into the pathophysiology of disease. In addition, genomics encompasses the use of genetic study to develop newer therapeutic interventional strategies.

Disease Classification

Functional genomics shifts the classification of diseases from a clinical description, or phenotype, to a genetic description. This new genetic classification system helps to explain variations in course, treatment, and presentation as the result of differences in patterns of inheritance and gene expression.

Disease Testing

New diagnostic tests have been developed thanks to the HGP. In these testing strategies, DNA, RNA, chromosomes, and proteins are analyzed with the intention of detecting inheritable disease and identifying mutations to aid in diagnosis and improve prognostication. Genetic screening tests are now commercially

available to help detect various cancers, LHON, and age-related macular degeneration (ARMD).

Prescribing Pharmaceuticals

In the future, it may be possible to evaluate a patient's genotype to best match the patient with medication. Known as pharmacogenics, the study of how DNA variations affect the body's response to drugs will help the clinician to choose a safe and effective medication tailored to each individual patient. This concept should not be considered too radical, because optometrists already are well aware of how the use of topical steroids can cause elevation in intraocular pressure in patients with a certain genetic profile.

Gene Therapy

This form of therapy seeks to deliver nucleic acids to alter or prevent a pathological process. Gene therapy makes use of a carrier, usually a virus, impregnated with genetic information. Infection of the harmless virus causes insertion of a new strand of DNA into the genome of the patient with the expected result of altered protein production. In this way, genetic diseases caused by the absence of a certain protein may be cured by the insertion of a strand of DNA into the genome to cause production of the deficient protein. To this end, the goal of gene therapy is the lifelong replacement of the missing gene product. Nonviral vectors, usually chemicals complexed with nucleic acids, may also be used for the transfer of genetic information to the patient. Nonviral vectors are safer but less effective than viral vectors.

GENETICS OF SELECTIVE SYSTEMIC DISEASES

Systemic Hypertension

Genetics plays an important role in the development of systemic hypertension. Correlation of blood pressure readings within a family helps to clarify the inheritance factors involved with elevated systolic and diastolic pressures. Inheritance in this case is multifactorial. For example, certain genes that produce systemic diseases also are associated with increased arterial blood pressure. Little consistency exists in the studies, however, and several genetic factors appear to come into play. Identification of a single gene responsible for blood pressure does not seem likely, and it is thought that several genes control various aspects of the maintenance of systemic arterial pressure. For example, genes have been identified that control angiotensin, angiotensin-converting enzyme, angiotensin receptor 1, and two hypertension susceptibility locuses.

Atherosclerosis

Most of the genetic factors underlying atherosclerosis have yet to be discovered. A genetic predisposition towards early damage to the arterial wall appears to exist, as is shown by the early development of heart disease within families. Genes have already been identified that control the low-density lipoprotein receptor, the homocysteine level, and the plasminogen-activator inhibitor.

Diabetes Mellitus 1 and 2

Multiple genes control type 1 diabetes mellitus (DM). A mandatory inheritance of a sufficient complement of genes to confer susceptibility to the disease appears to exist. As yet unidentified modifying factors account, in part, for the fact that among identical twins, when one twin gets type 1 DM, only half of the siblings get the disease. The major susceptibility gene for type 1 DM is located in the human leukocyte antigen (HLA) region on chromosome 6. Many patients with type 1 DM have the HLA DR3 or DR4 haplotype. At least 17 different genetic loci contribute susceptibility to type 1 DM. Still, many patients with these haplotypes never develop type 1 DM. Genes have been identified that control insulin, the cytotoxic T lymphocyte immune response responsible for type 1 DM, and the production of glucokinase.

Type 2 DM is strongly influenced by genetic makeup, and 90% of identical twins with type II DM will involve both siblings. If both parents have type II DM, then there is a 40% chance that the offspring will develop the disorder. Genes help to control the action of insulin, the receptors for insulin and the enzymes involved in glucose metabolism. Genes have been found that control the insulin promoter factor, the insulin receptor substrate, the sulfonylurea receptor, growth hormone and many other factors related to insulin regulation.

GENETICS OF SELECTIVE OCULOSYSTEMIC DISEASES

The HLA-B27 allele, or haplotype, was originally defined as a serological determinant, and comprises a family of nucleotide sequencing. HLA-B27 is highly associated with ankylosing spondylitis (AS) because 90% of patients with this spondylarthropathy have the B27 marker. Approximately 75% of patients with reactive arthritis (ReA), formally known as Reiter's syndrome, also have the B27 marker. In addition, approximately 50% of patients with Crohn's disease have this same allele. Strong evidence suggests that the B27 molecule is actively involved with the disease pathogenesis.

Among the collagen-vascular diseases, juvenile rheumatoid arthritis (JRA) is associated with the HLA-DR8 and -DR5 allele. Sjögren's syndrome is associated with the HLA-DR3 haplotype, and systemic lupus erythematosus (SLE) is associated with HLA-DR3.

Other genetically driven immune diseases include Graves' disease (B8), myasthenia gravis (B8 and DR3), multiple sclerosis (DR2), and acute anterior uveitis (HLA-B27).

GENETICS OF SELECTIVE OCULAR CONDITIONS

Retinitis Pigmentosa

This group of retinal dystrophies can be inherited as an autosomal dominant, autosomal recessive, or X-linked trait. RP can result from mutations on various chromosomes, including the X chromosome.

Glaucoma

Various susceptibility genes have been identified for specific types of glaucoma. More than 25 gene loci have been identified for the glaucomas, and individual genes for some have been discovered. At least 54 variations of the myocilin gene have been found to be associated with primary open-angle glaucoma (POAG). Other genes, such as the optineurin (OPTN) gene, have also been found associated with POAG.

Age-Related Macular Degeneration

Mutations in the gene ABCA4 are associated with ARMD development. This gene is also involved in the development of Stargardt's disease. The gene is associated with the production of proteins found in the rims of the rod outer segment discs (rim proteins).

INCORPORATING GENOMICS INTO THE PRACTICE

Wormington (2004) suggests eight ways to incorporate genetics and genomics into the optometric practice. These eight methods are summarized in the text that follows.

Education

1. First, the optometrist can identify the most common systemic and ocular pathologies most common to the practice and learn the genetics and genomics underlying these diseases.
2. Next, the optometrist can learn how genetics affects the population encountered in the office and how the genes influence individual risk.
3. Finally, the optometrist can learn where to locate genetic information and resources.

Disease Involvement

4. The optometrist must begin to think of all diseases encountered in the office, with the possible exception of trauma, as having a genetic basis. In this way, the optometrist may begin to incorporate genetic thinking and philosophy into the delivery of eye care.
5. To this end, Wormington suggests that the optometrist administer a family history on all patients and draw up a family pedigree in select cases. This procedure will help clarify how a certain disorder, for example, diabetes mellitus, has run in the family.

Laboratory Testing

6. The optometrist may order and interpret specific genetic laboratory tests. As genetic testing for ocular diseases expands, the optometrist will want to keep abreast of the latest developments and learn which tests are most appropriate to order. The identification of significant genetic disease in the office, whether by examination or laboratory testing, should prompt a referral to genetic professionals.
7. To this end, the optometrist should develop a referral network to genetic counselors. These medical geneticists can help explain the ramifications of the disease to the patient and advise on the impact of the disease on future generations.
8. The optometrist must be cognizant of the moral, social, and legal issues raised by the new fields of genomics and molecular optometry.

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CHAPTER 24

Nutrition and the Eye

CHAPTER OUTLINE

The past few decades have marked a period of rising interest and intense research into the impact of nutrition on ocular tissue toxicity and disease. Although anecdotal reports have surfaced during the past century indicating that delay or even amelioration of certain eye conditions could be achieved through the use of diet and nutritional supplements, the finding that tissue damage can occur by oxidation spurred the recent spate of medical studies into this realm. Such free radical damage to tissues was found to be at the basis of some eye diseases. Researchers then discovered that these free radicals could be "swept up" and their effects neutralized by the antioxidant effects of certain vitamins, minerals, and other compounds.

Once these observations were confirmed, the nutritional impact on ocular disease began to make sense, and this once medically ignored area was thrust into the global spotlight. No longer scoffed at by the majority of medical educators, researchers, and clinicians, nutritional intervention into eye and systemic diseases is achieving greater interest and funding, leading to credible scientific and medical research. Therapeutic criteria researched and confirmed by some of the world's most conservative medical institutions now routinely include findings concerning the impact of diet and nutritional supplementation on certain ocular diseases.

The impact of environmental and lifestyle choices on eye disease is not to be ignored. Although genetics plays the most important role in the evolution of disease, this risk factor cannot be modified, and thus research is concentrating on environmental influences and lifestyle choices and their impact on pathology. For example, free radicals can be produced by such environmental influences as toxic chemicals in the air, food, water, and by overexposure to ultraviolet light. In addition, lifestyle choices regarding obesity, smoking, and sun tanning have been found to produce free radicals, prevent antioxidant effects, and result in tissue damage.

This chapter focuses on four leading areas of research and new therapeutic regimens in ocular disease and nutrition: cataract, dry eye, vitamin-A deficiency, and age-related macular degeneration (ARMD).

NUTRITIONAL INFLUENCES ON CATARACT FORMATION

The Physiology of Cataract Development

The clarity of the human lens is the result of tightly controlled placement of lenticular fiber cells. Within each fiber cell are genetically produced crystallins that, at the molecular lever, are packed and organized to further enhance transparency. Such cellular organization provides a virtually uninterrupted pathway for photons streaming towards the retina.

The aging lens encounters significant stresses that challenge its function to remain clear. Physical, genetic, phototoxic, and chemical damage can all alter lenticular proteins, resulting in the formation of precipitates within the lens. These proteinaceous aggregates disrupt the tight packing of fiber cells and disturb the orderly arrangement of molecular crystallins, resulting in cataractous opacities.

Cataracts are visible as inclusions, bubbles, whorl-like clouds or sparkling deposits within the otherwise clear matrix of the lens. Light rays become scattered as photons reflect, refract, or are absorbed by cataracts. A reduction in visual acuity, contrast sensitivity and color discrimination occurs as a result.

Of all the cataract risk factors that have been identified, age plays such a significant role that a common assumption is that virtually all humans will develop cataracts given enough time. The aging lens develops cataracts from a host of insults, however, including acquired systemic diseases, genetic disorders, phototoxicity, nutrition deprivation, and chemical exposure.

Surgical treatment of cataract remains one of the most successful and common operations performed in the United States today, and the rate of undesirable outcomes is remarkably low. Nonetheless, cataract development remains one of the world's leading causes of blindness, especially in developing nations, and surgery in these areas is often too expensive or not available. A therapeutic regimen that may forestall cataract development for life of the patient is therefore desirable. Although pharmaceutical research in this area has been ongoing for four decades, nutritional intervention to prevent or slow the development of cataract may provide a safe, economical, and effective therapy.

The Pathogenesis of Cataract Development

Both light and oxygen are implicated in the creation of reactive forms of oxygen, a fact that has been supported by several studies. Known as oxidative stress, this process occurs because of the presence of free radicals, which are singlet oxygen and superoxide molecules with unpaired electrons. Free radicals attack protein and lipid molecules in tissues in an attempt to scavenge an electron, and in the process they damage mitochondrial DNA. This damage at the level of DNA interferes with cellular processes that can result in disease. Free radicals can be produced by both light and oxidative metabolism.

The incidence of cataract has been positively correlated to the intensity and duration of sunlight exposure. In the laboratory, the human lens can be induced to form cataract under a high oxygen atmosphere. These two observations support the proposal that light and oxygen are implicated in the creation of free radicals that result in cataract. These reactive forms of the oxygen molecule are most likely found in the aqueous humor, the vitreous humor, and the lens itself.

Tissue toxicity can be caused by the relatively high oxidizing power of oxygen. The oxygen radical may be produced by photochemical reactions during daylight hours and nonphotochemical reactions under dim illumination or sleep. When lenticular fibers are damaged, the cell membrane's ability to transport certain ions is reduced. This process results in physiological damage.

Risk Factors in Cataract Development

Oxygen radical damage to the lens can result from extended sunlight exposure, cigarette smoke, x radiation, and high levels of oxygen.

People living at high altitudes or closer to the equator are exposed to greater light levels. These populations have an increased risk of certain forms of cataract. These elevated light levels alter lenticular proteins that precipitate out as cataracts in the lens. Ultraviolet radiation in the range of 290 to 320 nm (UV-B light) may contribute to the formation of age-related cataracts. Although studies remain inconclusive, a strong relationship appears to exist between UV-B and age-related cortical cataracts.

In addition to elevated light levels, high-energy radiation exposure increases the rate of cataract development. This increase has been shown to be a dose-response relationship, and in at least one study, patients undergoing whole-body irradiation developed cataracts earlier than the unradiated population. As in the case of light exposure, it appears that lenticular proteins are altered by high-energy radiation that precipitates to cause cataracts.

Clearly, elevated levels of oxygen can cause cataracts, and these levels are achieved in patients receiving hyperbaric oxygen therapy. In experiments with mice, the incidence of mature cataract was markedly elevated in a group exposed to 100% oxygen for 3 hours twice weekly. As with light and x radiation, oxygen contributes to lens protein

alteration and accumulation, and eventual cataract development.

Smoking is one of the most important amenable risk factors in cataractogenesis. Smoke contains significantly harmful chemicals, including arsenic and lead, and poisonous gases, such as carbon monoxide and hydrogen cyanide. These compounds are cataractogenic in two ways: first, they neutralize the physiological mechanisms that counteract oxidation, and second, the systemic absorption of these compounds may allow their accumulation within the lens, leading to the oxidative changes causing cataract. Studies do show an association between smoking and cataract formation. One study showed an increased chance of developing nuclear sclerosis associated with an increased chance of pack-years of smoking.

Primary Physiological Defense Mechanisms

Oxyradical damage can be partially negated or delayed by the presence of tissue-based enzymes that act to prevent toxicity. Superoxide dismutase is present in the epithelium and cortex of the lens and is the first line of lens defense against oxidation. Other enzymes, such as catalase and glutathione peroxidase, also prevent oxyradical tissue damage of the lens epithelium and cortex.

In addition to lenticular enzymes, ascorbic acid (vitamin C) is present in the aqueous at a concentration approximately 20 times the plasma concentration. Ascorbate can protect the lens membranes from oxyradical damage. One study showed that the brown color in lenses exposed to ultraviolet light is minimized by ascorbate. With age, lenticular ascorbate decreases, with a consequential increase in opacification. Research has found that the concentration of ascorbate in the lens can be increased by an oral consumption of vitamin C.

Vitamin E (tocopherol) is a lipid-soluble antioxidant that helps maintain tissue integrity. Studies have shown vitamin E helps delay a variety of induced cataracts in animals.

Secondary Physiological Defense Mechanism

A second system has been discovered that is defensive against oxyradical damage. This proteolytic system helps to degrade and eliminate damaged and obsolete proteins and other biomolecules from the lens. The aging lens undergoes oxidative stress with a concurrent reduction of the proteolytic system. When this secondary defense mechanism fails with age, and the antioxidative enzymes become damaged by photooxidation, damaged proteins accumulate in the lens.

Nutritional Influences on Cataract Development

Vitamin C

An increase in dietary ascorbate raises the eye tissue ascorbate concentration. One study showed that vitamin C intake reduced the risk of nuclear sclerosis but increased the risk of cortical cataract. Most studies confirm, however, that an increase in vitamin C intake is related to a decrease in cataract formation.

Vitamin E

Tocopherol has antioxidant capabilities that are enhanced by the presence of vitamin C. Studies have shown a lower prevalence of cataract in participants who consumed vitamin E supplements.

Carotenoids

The best known of the roughly 400 carotenoids is beta-carotene, a lipid-soluble strong antioxidant. Studies have failed thus far to demonstrate an association between some of the carotenoids and a lowered risk of nuclear sclerosis, except in men who smoke. In women, however, high levels of plasma carotenoids were found to increase the risk of certain forms of cataract.

Multivitamins

Most studies showed a decreased prevalence of various forms of cataract in users of multivitamins that contain antioxidant combinations.

Patient Education

Relatively few studies have been performed on the nutritional and lifestyle choices that can mitigate cataract formation. With data from the few studies in existence, we may advise patients to do the following:

- Control light exposure and, in particular, UV-B exposure to the lens by use of UV-absorbing sunglasses and the wearing of wide-brimmed hats when outside in sun, snow, or beach conditions.
- Take not more than 250 mg/day of vitamin C to maximize plasma saturation, while minimizing the potential cataractogenesis risk of vitamin C when it acts as a carbohydrate.
- Take 200 IU of vitamin E daily (not to exceed 200 IU/day because of a recent study showing possible heart-health issues at levels of vitamin E exceeding 400 IU/day).
- Reduce caloric intake to reduce overall body mass.
- Reduce carbohydrate intake, because these sugars have been implicated in cataract formation in diabetics.
- Smoking cessation is necessary, as well as reducing second-hand smoke from family members within a shared household. Smokers require special education and encouragement to end their smoking habit.

- Consume foods rich in antioxidants, including spinach, broccoli, kale, carrots, cantaloupes, and green peppers.
- Diabetics are at a much greater risk of premature cataract development and require education on adapting a healthy lifestyle emphasizing antioxidant dietary intake and tight serum glucose control.
- Alcoholics are particularly noncompliant and thus require intensive patient education emphasizing healthy nutritional intake.
- Avoid x radiation near the head and neck if possible, but the risk/benefit ratio is often in favor of life-improving and life-saving radiological imaging.

NUTRITIONAL INFLUENCES ON DRY EYE

The role of tears in maintaining a healthy ocular surface environment is multifactorial and complex. Once thought to be a simple lubricant, tears have since been found to contain epidermal growth factor and vitamin A, which both allow for healthy maintenance of the surface epithelium. Without these factors, surface diseases such as squamous metaplasia and infections, can occur. A lack of tears, called dry eye, produces an unhealthy surface environment, which prevents corneal epithelial healing.

Dry eye is now classified as dry eye caused by tear deficiency or dry eye secondary to increased tear evaporation. Two types of tear-deficiency dry eye exist: Sjögren's syndrome (SS)-type dry eye, or keratoconjunctivitis sicca (in which a lack of basic and reflex tears is present), and non-SS dry eye (which delivers occasional reflex tears).

Treatment Modalities in Dry Eye

Punctal Plugs

At present, SS dry eyes is treated best with occlusion of the puncta. In this way, active components of the tears, such as epidermal growth factor (EGF) and vitamin A, are retained on the ocular surface for a longer duration. Epidermal healing is promoted in this way.

Artificial Tears

Because artificial tears do not supply vital factors found in tears, persistent epithelial defects do not respond to this form of treatment. Artificial tears are effective in post-LASIK surgery dry eye, however. In post-LASIK dry eye, the microkeratome used to create the corneal epithelial flap severs nerves essential for lacrimation. This produces a chronic superficial punctate keratopathy secondary to the poor tear film. Artificial tears, punctual plugs and cyclosporine ophthalmic emulsion (RESTASIS, .05% 1 gtt bid), are the treatments of choice in this situation. TheraTears (Advanced Vision Research) causes increased conjunctival goblet (mucus-producing) cell density in rabbits with keratoconjunctivitis sicca.

Vitamin A

True vitamin A deficiency is rare in the United States, but surface epithelial defects do respond to oral vitamin A therapy by increasing mucus production of the goblet cells. In studies, topical vitamin A (VIVA-DROPS, VISION Pharmaceuticals) provided some reduction in the signs and symptoms of dry eye in some cases.

Vitamin B_{12}

Topical vitamin B_{12} (NutraTear, Aqueous Pharmaceuticals) is an antioxidant and can increase the rate of epithelial healing in rabbit cornea. More studies are needed in this area before specific recommendations are made, however.

Cyclosporin

Cyclosporin A (RESTASIS) can stimulate tear production by suppressing inflammation. Results from studies show improvement of the signs and symptoms of dry eye, but the economic challenge of this new generation of topical dry eye drops may hinder its widespread use.

Oral Supplementation in Dry Eye

Flax Seed Oil

Although unsupported by any credible scientific study as of this writing, anecdotal evidence points to a role for oral flax seed oil supplements in the treatment of dry eye complaints. Flax seed oil has been used for treatment of post-LASIK dry eye, and patients have personally reported relief of dry eye symptoms to this author. One capsule twice daily with a meal is often prescribed for dry eye or after LASIK treatment.

Fish Oil

Fish oil (a potent antioxidant) capsules, often combined with flax seed oil, have been used in the treatment of dry eye. Anecdotal evidence points to symptomatic relief of dry eye. To reestablish an ocular environment conducive to successful contact lens wear, this author has successfully treated cases of dry eye secondary to thyroid disease with oral flax seed and fish oil supplementation. A dearth of credible scientific studies on the effect of oral fish oil and flax seed oil on dry eye exists as of this writing, however.

NUTRITIONAL INFLUENCES ON VITAMIN A DEFICIENCY

Although rare in the United States, vitamin A deficiency is prevalent worldwide and affects as many as 228 million children. One of the four leading causes of

preventable blindness in the world, vitamin A deficiency is caused by poor diet, malabsorption syndrome, and Ross River disease.

Chronic deficiency of vitamin A results in a wide range of ocular conditions known as xerophthalmia. The first and most common sign of vitamin A deficiency is reversible night blindness. Typically, regeneration of rhodopsin in the retina allows for fast visual recovery after exposure to bright light. Vitamin A deficiency causes a slow regeneration of rhodopsin, yielding a condition of night blindness. This condition is reversible in its earliest stages with oral vitamin A supplementation.

With prolonged vitamin A deficiency, yellow and white dots appear in the peripheral retina, which represent retinal damage. These focal retinal pigment epithelium (RPE) defects are reversible with vitamin A supplementation.

In cases of prolonged vitamin A deficiency, instability of the tear film causes drying of the conjunctiva and cornea. This condition is known as xerosis and results in a thickened and modified corneal and conjunctival epithelium. Loss of goblet cells occurs with a concurrent loss of mucus. Keratinized conjunctival paralimbal gray deposits, known as Bitot's spots, form around the cornea. Prolonged dryness causes corneal epithelium disruption and eventual ulceration. Severe corneal alteration results in keratomalacia and scarring with permanent visual loss.

Treatment of Vitamin A Deficiency

Once vitamin A deficiency is confirmed with plasma vitamin A levels, then vitamin A supplementation is used to reverse night blindness, xerosis, and Bitot's spots. Corneal complications are less amenable to vitamin A supplementation, and topical vitamin A ointment has not been shown to be a beneficial treatment in studies.

Treatment of xerophthalmia consists of 200,000 IU of vitamin A daily for 2 days, followed by another 200,000 IU dose 2 weeks later.

NUTRIONAL INFLUENCES ON MACULAR DEGENERATION

Macular Degeneration Risk Factors

Sunlight as a Stress

Photooxidative stress plays a significant role in degenerative changes in the macula. Sunlight is a significant environmental source of oxidative damage to the retina. No study has confirmed a relationship between sunlight and ARMD, but studies have shown an increased risk of ARMD with higher lifetime exposures to sunlight. Obviously more studies are needed to reconcile this discrepancy.

One possibility is that ARMD occurs because of photooxidative stress to the outer retina (nearest the retinal pigment epithelium) from blue light. No evidence exists as of this writing of any relationship between ultraviolet light and ARMD, particularly because almost all of the UV spectrum is absorbed by preretinal ocular structures. Visible light, and in particular blue light, is implicated in some studies as a potential contributor to ARMD, however.

Age as a Stress

The physiological mechanisms of retinal repair may decrease with age, and this fact may contribute to ARMD. In one study, recent sunlight exposure in the older population was linked to geographic atrophy, which is not found in the younger population (geographic atrophy is associated with ARMD). Thus, the young have repair mechanisms that prevent geographic atrophy, but with age these mechanisms fail to prevent such damage. After sun exposure, age is the strongest predictor of ARMD, but, regrettably, is not modifiable.

Smoking as a Stress

Smoking increases oxidative stress to the macular tissues and reduces the antioxidative compounds in the plasma. Smoking has been found to reduce vitamin C and carotenoid blood levels, as well as reducing macular pigment density. In addition, smoking causes vasoconstriction of local blood vessels and hypercoagulability of the blood, both of which may contribute to a vascular cause of ARMD. Studies offer conflicting data to support a causal relationship between smoking and ARMD. The strongest relationship to emerge from all studies is between current smoking and exudative ARMD. Little association exists between smoking and early ARMD. One possible reason that most people who smoke don't get ARMD is that particulate matter and gases in smoke interact with genetic factors to produce an ARMD response.

Clinical Features of Age-Related Macular Degeneration

In ARMD degeneration of the outer layers of the macula occurs, with death of photoreceptors and sometimes neovascularization. The lesions of ARMD occur between the photoreceptor (rod and cone) layer and the choroids. Histiologically, Bruch's membrane thickens, pigmentary disturbances occur in the RPE, and the photoreceptors can atrophy, with possible neovascularization.

Clinically, drusen are deposited between the basal lamina of the RPE and the inner membrane of Bruch's membrane. The critical characteristics of ARMD are large, soft, and confluent drusen. This type of drusen increases the risk of severe ARMD.

In late ARMD, atrophy of the RPE, known as geographic atrophy, or "dry" ARMD, occurs. Neovascularization arises from the choroids and penetrates through Bruch's membrane. These blood vessels may leak, causing sensory retinal detachment or hemorrhage. This is the clinical picture of "wet" ARMD.

Causes of Early Age-Related Macular Degeneration

Drusen

The earliest two changes in ARMD are soft drusen from the RPE and pigmentary abnormalities of the RPE. Histiological changes in the RPE occur because of age and include changes in their microvilli. Normally, the RPE acts to digest waste products from the photoreceptor outer segments. In ARMD, however, undigested waste products from the photoreceptor outer segments accumulate, causing drusen deposits. Drusen blocks nutrients originating in the choroidal capillaries from reaching the RPE causing the eventual demise of RPE cells and photoreceptors.

Photooxidative Stress

The macula is partially vulnerable to oxidative stress because of its high oxygen demand and light exposure. Both light and oxygen combine to create an environment of free radical production and subsequent damage. Studies tend to support a role for oxidative stress in the production of ARMD.

Vascular Pathology

Arteriolar sclerosis of the choriocapillaris has been proposed as a contributor to ARMD, but some researchers feel that these vascular changes are secondary to RPE degeneration.

Immune Response

Because researchers have identified immune products such as immunoglobulins lining Bruch's membrane, recent proposals suggest a role of the immune system in ARMD. The thickening of Bruch's membrane with age, and an associated immune system degradation of the membrane may conspire to promote ARMD.

Nutritional Intervention in Age-Related Macular Degeneration

Relatively few studies to date produce significant evidence for nutritional intervention in ARMD. Nutrients that may delay progression of ARMD include antioxidants, dietary fatty acids, carotenoid plant pigments, and essential minerals and enzymes.

Antioxidants

These compounds scavenge reactive oxygen molecules and convert free radicals to nonreactive compounds. These include vitamin C, vitamin E, and carotenoids. Vitamin E is highly concentrated in the retina and oral supplementation (in animals) increases vitamin E concentration in retinal photoreceptors. Vitamin E from dietary sources (gamma tocopherol) appears to have a more significant role in antioxidative processing than vitamin E from supplementation (typically alpha tocopherol). The link of oxidative damage from light sources and vitamin C is weaker than with vitamin E.

Carotenoid Plant Pigments

Lutein is a xanthophyll carotenoid pigment found in the macula, which absorbs blue light and acts as an antioxidant sweeping up free radicals. High-dose lutein supplementation and an intake of food sources of lutein have been found to increase macular pigmentation. Although leucopenia is the carotenoid that best scavenges free radical singlet oxygen, it theoretically would be protective against ARMD, but it is not found in the retina.

Minerals and Enzymes

Essential minerals (zinc and copper) and enzymes (catalase, superoxide dismutase, and glutathione peroxidase) help quench radicals and convert toxic chemicals to nontoxic forms. If adequate levels of these minerals and enzymes are present in the diet, additional supplementation will not add further protection.

Fatty Acids

Evidence exists that diet alterations cause changes in retinal lipids. For example, fish oils fed to rats seem to protect against light-induced damage. In one study, high levels of linoleic acid found in vegetable oils seemed to increase the risk of "wet" ARMD. Studies indicate that saturated fat increases the risk of ARMD.

Age-Related Eye Disease Study

This National Institutes of Health (NIH) study assessed factors relating to ARMD. The study showed that "people at high risk for the development of advanced stages of ARMD lowered their risk by approximately 25% when they were treated with a high dose combination of vitamin C, vitamin E, beta-carotene and zinc."

These nutrients reduced the risk of visual loss in patients with moderate-to-advanced ARMD in one eye but not the other by 19%. Supplementation was not found to be beneficial in patients with no sign of early ARMD.

Summary of Recent Age-Related Macular Degeneration Nutrition Intervention Studies

Nutritional supplementation in ARMD remains controversial despite the findings of the Age-Related Eye Disease Study (AREDS).

The retina contains physiological mechanisms that counteract damaging free radicals, but these mechanisms diminish with age. It is hoped that dietary supplementation will counter this age-related impairment of physiological protection.

Besides the AREDS study, Richer in 2002 showed improvement of ARMD in his "LAST" study, which demonstrated the effectiveness of lutein and various antioxidants. Earlier in 1998 Newsome showed improvement of ARMD with zinc supplementation. Yet four additional studies showed no improvement of ARMD with supplements of vitamin E, vitamin C, buphenine, and zinc (Stur, 1996).

Lutein appears to protect the retina by filtering out blue light (Bartlett and Eperjesi, 2003) and by acting as an antioxidant (Bartlett and Eperjesi, 2003).

Patient Education

- Cigarette cessation reduces free radical intake and production and allows for increased antioxidant concentrations.
- Avoid exposure to bright sunlight. Wear UV-absorbing sunglasses and wide-brimmed hats to reduce blue light exposure to the macula.
- Control cardiovascular and hypertensive disease. This intervention may mitigate arteriosclerotic changes within the blood supply to the choriocapillaris. Improvement of vascular disease by diet, exercise, and medication increases oxygen delivery to the RPE and waste removal from the RPE.
- Increase intake of dark-green, leafy vegetables. Such vegetables as spinach, broccoli, and kale can increase intake of antioxidants. Caution should be taken in prescribing and intake of dark-green, leafy vegetables to patients on blood thinners (such as warfarin) because the high concentration of vitamin K in these plants can interfere with these medications. Usually, an intake of three spinach salads per week is recommended.
- Multivitamin supplementation. A multivitamin with vitamin C, vitamin E, beta-carotene, zinc, and lutein can help promote the intake of antioxidants.
- Limit animal fats to reduce free radical production, obesity, and vascular disease.
- Lower caloric intake to reduce free radical production, obesity, and vascular disease.
- Consume a diet rich in fruits, vegetables, and fish oils.
- Increase the intake of nuts rich in omega-3 and omega-6 fatty acids, such as walnuts, hazelnuts, almonds, and pecans.

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CHAPTER 25

Ophthalmic Care of the Pregnant Patient

CHAPTER OUTLINE

Pregnancy can induce radical changes to the eye. The optometrist must take care not to harm the mother or fetus when performing an ophthalmic examination or when treating the mother's eye disease. Physiological changes may occur to the tear layer, cornea, and the ocular tissues involved in intraocular pressure maintenance. Pathological conditions associated with or exacerbated by pregnancy include retinal and neurologic diseases. Topical medications may induce systemic manifestations in the mother-to-be and may potentially threaten the pregnancy or the fetus. This chapter reviews the alterations of the normal ocular physiology and the eye diseases associated with pregnancy.

DOCTOR-PATIENT INTERPERSONAL COMMUNICATION

One of the most challenging aspects of taking a history is the attempt to uncover whether a woman is pregnant. The asking of such a question at first seems fairly straightforward, however, experience will confirm that offense might be taken if the patient feels that the questioner is implying that she is obese. Nonetheless, the question must be posed to all patients who are about to undergo any optometric examination and treatment with topical medications, because these can have serious medical ramifications to the mother and fetus. In addition, the examiner will wish to display appropriate sensitivity when raising this question, because the patient may be have issues concerning weight, the loss of a fetus or child, or the inability to conceive.

One way to preserve the effectiveness of the doctor-patient bond without risking offense is to have the patient fill out a checklist that includes a question about pregnancy. This method avoids the patient thinking that she is being singled out by the doctor and asked about pregnancy because of her appearance. Despite a woman's age, she must be asked about pregnancy, and the checklist history avoids embarrassment when the very young teenager or the senior citizen is being examined.

One problem with the checklist is that it is impersonal, and does not strengthen the doctor-patient bond. Thus, another effective technique is to ask the female patient if she has any known medical condition, such as pregnancy, for which she is seeking medical care. By wrapping the central issue of pregnancy in the guise of other medical care, the patient realizes that the question of pregnancy is not being raised because of her personal appearance.

The examiner must determine whether the pregnant patient is smoking or using drugs and counsel against such behavior during pregnancy.

PHYSIOLOGICAL ALTERATIONS

Changes in the Tear Layer

Complaints of dry eye may occur during pregnancy, particularly in contact lens-wearing patients. Alterations in the normal tear structure are most likely the result of the dramatic hormonal changes that occur during this period of time. Topical staining may reveal stippling of the corneal epithelium, or, in more serious cases, a florid superficial punctate keratopathy. This condition of keratitis sicca is temporary, and should resolve after delivery, although it may persist during nursing. Artificial tear substitutes may reduce the symptomology of the sicca condition, but oral flax seed or fish oil capsules for the control of the dry eye should only be used with her physician's approval. The dry eye condition makes the use of contact lenses problematic, and may force the mother-to-be to reduce or discontinue wear. This situation can be a significant psychological challenge, because she may already be experiencing severe stress and anxiety. It is important to stress that the condition is temporary and contact lens wear may resume after delivery or when nursing has ended. Excess mucus production may also occur during pregnancy, causing transient blurring of vision. This condition resolves after delivery.

Changes in the Cornea

Pregnancy affects the cornea in three ways: it thickens, changes shape, and decreases in sensitivity. All these changes can alter visual acuity, refractive error, and contact lens wear. During pregnancy the cornea tends to thicken, most likely because of a generalized systemic edema that induces corneal uptake of fluid. This corneal edema reduces corneal sensitivity and can adversely affect contact lens wear. The thickened cornea is associated with an increase in corneal curvature, and these factors change the refractive error of the patient so that the patient may experience reduced visual acuity with her present spectacles or contact lenses. The fitting of contact lenses should be avoided until 1 month after delivery or after nursing has ceased. In addition to the above, a higher rate of pigmentary deposit in the shape of a Krukenberg's spindle has been observed in pregnant women. This condition may be the result of hormonal changes that cause pigmentary migration to the aqueous with eventual deposition onto the corneal endothelium.

Changes in Accommodation

A reduction in accommodation during pregnancy may occur caused by a thickening of the ciliary body because of fluid retention. A low-plus spectacle for near work may help the patient during this period. Accommodation usually returns to normal after delivery, but may be permanently reduced in presbyopic individuals.

Changes in Intraocular Pressure Maintenance

Hormonal changes increase the facility of the uveoscleral outflow mechanism and thus decrease intraocular pressure during pregnancy. The reduced intraocular pressure decreases in the second half of the pregnancy and may persist for several months after delivery. Another explanation for the reduced intraocular pressure is a decrease in the episcleral venous pressure.

PATHOLOGICAL CONDITIONS

Dermatological Disease

Chloasma

Typically a brown, blotchy, and flat hyperpigmentation, this skin change is a painless hypermelanosis of the skin around the eyelids. Known as the "mask of pregnancy," chloasma usually fades within a few months after delivery. Chloasma is most likely the result of high estrogen and progesterone levels.

Spider Angiomas

These reddish-purple spidery superepithelial blood vessel growths are painless and typically occur on the face and upper body. These growths are most likely the result of increased estrogen levels.

Eyelid Disease

Ptosis

Most cases of pregnancy-related ptosis of the upper lid are unilateral and related to fluid-retention or hormonal effects. Sleeping in a propped-up position will help reduce morning lid edema. Nonetheless, the spontaneous appearance of ptosis in any patient should elicit an immediate investigation to rule out a serious underlying neurologic entity. For example, Horner's syndrome may be more likely in the pregnant woman because of epidural analgesia used in delivery. Horner's syndrome and ptosis usually resolve within hours postpartum.

Retinal Disease

Pregnancy-Induced Hypertension

Typified by proteinuria, systemic hypertension, and peripheral edema, pregnancy-induced hypertension (PIH) may occur in the second trimester of pregnancy, usually after the 20th week. Once known as preeclampsia, PIH occurs in as many as 5% of healthy women during their first pregnancy. It is also more

common in multifetal pregnancy, very young or old maternal age, and in mothers who have vascular disease. This condition is serious because it can induce placental vascular insufficiency, thus threatening the viability of the fetus, and can even cause the death of the mother. PIH usually occurs spontaneously, but it may be brought about by medications. Topical medications such as epinephrine drops used for dilation of the pupil may induce PIH if absorbed systemically. PIH is diagnosed quickly by very elevated blood pressure readings in a pregnant woman. Extremely high systemic blood pressure can be associated with convulsions and is known as eclampsia. These PIH-associated convulsions usually occur later in the pregnancy and have an even more ominous prognosis than preeclampsia. Visual changes that include diplopia, scotomas, and blurred vision occur in 25% of preeclamptic women and 50% of eclamptic women. Retinal findings in PIH appear similar to hypertensive retinopathy and may include serous retinal detachments, retinal vascular occlusion, and yellowish opaque lesions of the retinal pigment epithelium. Ischemic optic neuropathy has occurred as a result of severe preeclampsia. Approximately 10% of women with PIH develop hemolysis, elevated liver enzymes, and low platelet count. Known as the HELLP syndrome, this PIH-related disorder may be associated with cortical blindness, vitreous hemorrhage, and serous retinal detachments. The visual findings usually resolve with swift and appropriate medical intervention. Because medications may induce PIH, topical epinephrine eye drops should be avoided when dilating the pupils of the pregnant patient. If such drops are necessary, as with the patient who complains of flashes and floaters or who requires intraocular surgery, then punctual occlusion for 1 to 2 minutes after insertion of the drops is recommended. This technique will minimize systemic absorption and reduce the risk of inducing PIH. Systemic management of PIH includes systemic blood pressure control, electrolyte imbalance control, and immediate delivery of the fetus if fetal maturity is appropriate.

Diabetic Retinopathy

According to the Diabetes in Early Pregnancy study (DIEP), diabetic retinopathy is most likely to progress in women with the poorest metabolic control over their serum glucose early in their pregnancy. In the study, this poor control was reflected in women with the best reduction in their HbA1c test. The dramatic improvement in the glycosylated hemoglobin ratio in these patients demonstrates that they had poor glucose control before pregnancy. The study found that the poorer the metabolic control of serum glucose during pregnancy, the faster the diabetic retinopathy progressed. Therefore, pregnancy worsens the course of diabetic retinopathy, sometimes to a significant degree. The DIEP study found that the state of diabetic retinopathy at the time of conception greatly influences the degree to which the retinopathy advances during pregnancy. For example, minimal baseline retinopathy at the time of conception, with just a few dot hemorrhages and less than 10 microaneurysms with no exudates, advanced to only an increase in microaneurysms in 8% to 21% of diabetic eyes. These cases of minimal baseline retinopathy at the time of conception never progressed to proliferative disease. In cases of mild diabetic retinopathy at the time of conception, however, 6% of cases did progress to the proliferative stage. Furthermore, in cases of moderate retinopathy at the time of conception, 29% of cases progressed to the proliferative stage. Axer-Seigel and others report that 26% of insulin-dependent diabetes mellitus patients with no retinopathy at conception developed mild nonproliferative diabetic retinopathy during the course of the pregnancy. Patients who develop gestational diabetes during pregnancy, however, are not at risk for diabetic retinopathy (although they do show an increased risk of developing diabetes mellitus later in life). Pregnant women who develop clinically significant diabetic macular edema (CSDME) usually have the edema resolve postpartum with improvement of their visual acuity. Patients with proliferative disease should have it treated by panretinal photocoagulation (PRP) before conception. A 26% lower rate of progression of diabetic retinopathy exists among women whose proliferative disease was treated versus those who did not receive such treatment. Although proliferative disease may regress after delivery, PRP should be used before conception or early in the pregnancy, because it reduces the risk of vitreous hemorrhage during delivery.

Central Serous Chorioretinopathy

Pregnancy-related hormonal changes may induce the exudation of fluid from capillaries under the macula. The fluid causes a neurosensory detachment of the macula with a resultant mild-to-moderate reduction of visual acuity. Usually the patient complains of a unilateral blurring of vision. A fundus examination may not be revealing as the sensory detachment can be subtle, but grayish-white subretinal exudates may be visualized in as many as 90% of pregnant women with central serous chorioretinopathy (CSC) within the area of the detachment. A photostress test usually reveals a delayed regeneration of photoreceptors that have been bleached out by intense light on the side with the CSC. Diagnostic fluorescein angiography is not necessary. Usually the detachment resolves within a few months after delivery with return of baseline visual acuity. Half of all cases of CSC during pregnancy occur in the third trimester.

Thrombotic Thrombocytopenic Purpura

A rare disease of unknown etiology, thrombotic thrombocytopenic purpura (TTP) is a usually fatal disease that occurs during pregnancy. TTP is characterized by hemolytic anemia caused by platelet destruction and consequential hemorrhaging. The patient may exhibit fever and malaise. Because subretinal fluid exudation may exist that results in complaints of blurred vision, the patient may seek out an eye specialist before seeing her physician. Ophthalmoscopy may reveal disc edema and retinal hemorrhages. Diplopia may result from paresis of the extraocular muscles. Any pregnant patient who is seen with diplopia or retinal hemorrhages is at risk for TTP and should be referred to her physician immediately for a serum analysis.

Disseminated Intravascular Coagulation

Unlike TTP, which causes an anemia secondary to platelet destruction, disseminated intravascular coagulation is a syndrome characterized by the development of fibrin clots throughout the small blood vessels of the pregnant patient. This condition results from activation of various clotting mechanisms and can cause blood clots to occlude the choriocapillaris of the choroids. This process can result in serous detachment of the retina and blurred vision. This clotting abnormality can be treated, and vision usually returns to normal once the systemic condition is resolved. This widespread thrombus formation is most often associated with complicated abortions, severe preeclampsia, and retained dead fetus.

Neurologic Disease

Pseudotumor Cerebri

Pseudotumor cerebri (PTC) is characterized by an elevation in intracranial pressure in the absence of a mass lesion of the brain. The etiology of PTC is often unknown, although it may be related to infection, obesity, intracranial obstruction, and various medications. Also known as idiopathic intracranial hypertension, the increased pressure gradient of the cerebral spinal fluid (CSF) yields a subtle, typically frontal headache. Mild blurred vision is often an early complaint. The patient may also experience scotoma, neck pain, and sixth-nerve palsy. Ophthalmoscopic evaluation typically demonstrates papilledema, with blurring of the disc margins in both eyes. During pregnancy, symptoms of PTC should elicit a concerted effort to confirm the presence of elevated intracranial pressure using MRI, lumbar puncture, CSF analysis, and ophthalmoscopy. PTC does not occur more commonly in pregnant women. The treatment of PTC is complicated in the pregnant woman, because medical intervention aimed at preservation of the visual field and symptomatic relief must be weighed against possible harm to the fetus. The typical treatment for PTC, weight loss, cannot be attempted during pregnancy. The optometrist must carefully document any visual field loss, and visual fields should be monitored monthly during pregnancy. If visual loss occurs, a short course of oral steroids during a 6-week period should help to prevent permanent field loss and still not harm the fetus. Another treatment for PTC, oral Diamox (acetazolamide), can be used only after 5 months of fetal gestation.

Multiple Sclerosis

Because multiple sclerosis (MS) peaks in women 20 to 40 years old, and occurs twice as often in women as in men, a significant number of pregnant women will have MS. MS is characterized by a demyelination of the nerves that supply the central nervous system. In this condition, loss of the protective myelin sheath that surrounds the nerve occurs, causing a disruption in electrical conduction. Consequently, paresthesia, memory loss, and loss of fine motor movements occur with the visual symptoms of diplopia, nystagmus, blurred vision, and field defects. The diagnosis of MS is made on the basis of magnetic resonance imaging (MRI) evaluation of the white matter of the brain and CSF evaluation. During pregnancy, MS attacks typically decrease and are less severe than normal. Postpartum, however, the attacks increase and are more severe during the first 3 months after delivery. The attacks then tend to stabilize to the rate typical before conception.

Pituitary Adenoma

These often microscopic and asymptomatic tumors of the pituitary gland grow more rapidly and become more symptomatic during pregnancy. Monthly visual fields are required during pregnancy to monitor any deterioration of the visual field. Medical use of bromocriptine (a dopamine agonist) can help tumor regression without adversely affecting the fetus.

Meningioma

This tumor is a slow-growing, well-encapsulated, and typically nonmetastatic lesion that is more common in pregnant women than in the general population. Because it can cause a variety of visual symptoms such as diplopia, blurred vision, and field defects, any pregnant woman with these symptoms should have a visual field and a referral to their obstetrician to rule out meningioma.

Pregnancy-Related Drug Interactions

Diagnostic Agents

The most significant diagnostic topical agent to avoid in the pregnant woman is phenylephrine. This medication, used diagnostically to dilate the pupil (with a

parasympatholytic agent), can exert a vasopressive effect. This in turn can lead to eclampsia and preeclampsia. In cases in which dilation is necessary for retinal evaluation of possible sight-threatening conditions (such as detachment), a 2.5% solution is advisable instead of a 10% solution. The higher concentrated phenylephrine has a greater chance of causing hypertension in the pregnant patient. Dilation of the mother to be is achieved most safely by the use of tropicamide, because both atropine and homatropine have been linked to birth defects, and scopolamine can cause tachycardia in the newborn infant. Topical anesthetics must be used with caution because no studies have been performed on these medications. Fluorescein dye can cause an allergic reaction in sensitive patients, and so should be avoided in pregnancy if possible. Fluorescein dye does cross the placenta and is also present in the breast milk for as long as 72 hours after administration, although no adverse fetal reactions have been observed.

Therapeutic Agents

During the typical 9-month gestation period, the pregnant woman may need topical medication to treat ocular disease. No medication is applied without risk, but the effect on mother and fetus may be minimized by punctal occlusion. If topical medications are necessary, then the following cautions should be understood:

- Phenylephrine. This topical medication may be used for therapeutic purposes in the breaking of posterior synechiae in cases of anterior uveitis. Because it has vasopressive effects, and its use may lead to eclampsia or preeclampsia, punctual occlusion is necessary. In addition, only the 2.5% form should be used in the pregnant patient, because the stronger 10% form has a much greater vasopressive effect. Unfortunately, the 2.5% form does not break synechiae as effectively as its stronger counterpart.
- Topical antibiotics. Topical polymyxin B and erythromycin have not been found to cause fetal damage and appear safe to use to treat bacterial conjunctivitis. Risk to the fetus cannot be ruled out when using any of the fluoroquinolones (such as ciprofloxacin and ofloxacin), because high dosages to test animals resulted in lower birth weight and skeletal abnormalities. Nursing mothers should be cautious not to use any fluoroquinolone, because the systemic form can be excreted through her breast milk.
- Topical antiviral agents. The risk cannot be ruled out when using mediations such as Viroptic (trifluridine), but animal studies have failed to reveal any problems. It is unknown whether Viroptic is excreted in the breast milk, thus the drop should be discontinued before nursing commences.
- Topical steroids. The risk to the fetus cannot be ruled out, and thus topical steroids should only be used with caution and punctal occlusion. The potential benefits may outweigh the potential risk particularly in cases of severe uveitis. In controlled animal experiments, topical steroids caused cleft lips and palates.
- Glaucoma drugs. Beta-blockers such as Timoptic (timolol maleate) can cause neonatal bradycardia and lowered blood sugar readings, and can occur in the breast milk. These drugs should be avoided during pregnancy, but the American Academy of Pediatrics has approved timolol to be used during lactation. Alphagan (brimonidine), a selective alpha-2 adrenergic agonist, shows no evidence of risk in humans, and is relatively safe to use in pregnancy. Alphagan can reach toxic levels in the breast milk and cause hypertension and apnea in children younger than 2 months, and thus should be used cautiously in lactating patients. The prostaglandins (travoprost [Travatan], bimatoprost [Lumigan], and latanoprost [Xalatan]) are a newer generation of glaucoma medications that have not been adequately studied as of yet. One small study of nine women failed to show any relationship between the use of latanoprost and an adverse outcome of pregnancy. Lactating mothers should use these with caution, because it is unknown whether the prostaglandin medication is excreted in the breast milk. The sulfonamides, such as the carbonic anhydrase inhibitors (CAI), medications that include acetazolamide (Diamox) and methazolamide (Neptazane), are potentially fetal-toxic and should be avoided during pregnancy. This warning may apply to topical CAI agents as well.

In general, all topical diagnostic and therapeutic agents should be avoided whenever possible during pregnancy and lactation.

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APPENDIX 1

Systemic Manifestations of Ocular Medications

DRUG BRAND NAME AND MANUFACTURER	GENERIC NAME	CLASSIFICATION	DESIRED EFFECT/ PURPOSE	SYSTEMIC SIDE EFFECTS
Azopt (Alcon)	Brinzolamide, 1.0% ophthalmic suspension	Carbonic anhydrase inhibitor	Decreases intraocular pressure (IOP)	Sulfonamide-type allergic (sulfa allergy) response possible, Stevens-Johnson syndrome, blood dyscrasias.
Betoptic S (Alcon)	Betaxolol HCl, .25%	Cardioselective beta-1-adrenergic receptor blocker	Decreases IOP	Bradycardia, bronchospasm in asthmatic patients, depression (rare); in rare cases lowers HDL cholesterol levels
Ciloxan (Alcon); Ocuflox (Allergan); Quixin (Santen); Vigamox (Alcon); Zymar (Allergan).	Ciprofloxacin, 0.3% HCl solution and ointment; ofloxacin, 0.3%; levofloxacin, 0.5%; moxifloxacin, 0.5%; gatifloxacin, 0.3%.	Antimicrobial fluoroquinolone	Eradication of bacteria	Dermatitis is rare, systemic fluoroquinolones can increase potential of warfarin blood-thinning effect (not seen topically yet).
Natacyn (Alcon)	Natamycin ophthalmic suspension	Antifungal	Eradication of topical fungal infections	No known systemic side effects
Patanol (Alcon)	Olopatadine HCl, 0.1% and 0.2% ophthalmic solution	H1 receptor antagonist, topical antihistamine with mast-cell stabilization	Acute allergic conjunctivitis	Headaches
TobraDex (Alcon)	Tobramycin and dexamethasone suspension	Antimicrobial bactericidal (aminoglycoside) and antiinflammatory	Bacterial ocular infection with inflammation	Rare with tobramycin, elevated IOP (after 3 weeks and rare) and cataract formation, slower corneal wound healing from steroid.

Continued

DRUG BRAND NAME AND MANUFACTURER	GENERIC NAME	CLASSIFICATION	DESIRED EFFECT/ PURPOSE	SYSTEMIC SIDE EFFECTS
Travatan (Alcon)	Travoprost 0.004% ophthalmic solution	Prostaglandin f2-alpha analogue	IOP reduction	Angina; flu-like symptoms; anxiety; joint pain; bradycardia; depression; (systemically the safest class of glaucoma drugs).
Albalon (Allergan)	Naphazoline, 0.1% HCl solution	Ocular vasoconstrictor	Topical allergy	Headaches, dizziness, hyperglycemia.
Alphagan P (Allergan)	Brimonidine tartrate, 0.15% solution	Selective alpha- 2 adrenergic agonist	IOP reduction	Insomnia, headache, fatigue, dry mouth, bradycardia, tachycardia (rare).
Betagan (Allergan)	Levobunolol HCl, 0.25% and 0.5%	Noncardioselective, beta-adrenergic receptor blocker	IOP reduction	Bronchospasm in COPD and asthma, bradycardia, possibly masks hyperglycemia and hyperthyroidism symptoms (rare); depression; lowers HDL level.
Bleph-10 (Allergan)	Sulfacetamide, 10% ophthalmic solution	Antibacterial and bacteriostatic	Bacterial conjunctivitis	Stevens-Johnson syndrome, aplastic anemia, blood dyscrasias.
Blephamide (Allergan)	Sulfacetamide, 10% solution and prednisolone acetate, 0.2% or 0.25%	Bacteriostatic and antiinflammatory	Superficial bacterial ocular infection with inflammation	Stevens-Johnson syndrome, elevated IOP, cataract formation.
Elestat (Allergan)	Epinastine, HCl 0.05%	Antihistamine	Topical allergy	Headaches, upper respiratory disease, sinusitis, cough.
FML Forte (Allergan)	Fluorometholone alcohol, 0.25% suspension	Steroid antiinflammatory	Inflammation reduction	Systemic hypercorticoidism, cataract, IOP elevation (less likely than other topical steroids)
HMS (Allergan)	Medrysone, 0.1% suspension	Steroid antiinflammatory	Inflammation reduction	Systemic hypercorticoidism, IOP elevation, cataract.
Lumigan (Allergan)	Bimatoprost, 0.03% solution	Prostaglandin analogue	IOP reduction	Upper respiratory cold, headaches, abnormal liver function tests.
Pred Forte (Allergan)	Prednisolone acetate, 1.0%	Steroid antiinflammatory	Inflammation reduction	Hypercorticoidism (rare), cataract formation, IOP elevation.

DRUG BRAND NAME AND MANUFACTURER	GENERIC NAME	CLASSIFICATION	DESIRED EFFECT/ PURPOSE	SYSTEMIC SIDE EFFECTS
Propine (Allergan)	Dipivefrin, 0.1% HCl	Prodrug	IOP reduction	Tachycardia, arrhythmia.
Zymar (Allergan)	Gatifloxacin, 0.3% solution	Bactericidal fluoroquinolone	Topical bacterial infection	Systemic administration of some quinolones increases potential of warfarin blood-thinning effect (not seen topically yet).
Alrex (Bausch & Lomb)	Loteprednol etabonate, 0.2% solution	Site-specific corticosteroid	Allergic topical antiinflammatory	Headaches, rhinitis.
Carteolol (Bausch & Lomb)	Carteolol HCl 0.1%	Nonselective beta-adrenergic blocker	IOP reduction	Bronchospasm, asthma, and COPD exacerbation; hyperglycemia and hyperthyroidism masking; bradycardia.
Lotemax (Bausch & Lomb)	Loteprednol etabonate, 0.5% ophthalmic suspension	Site-specific corticosteroid	Ocular inflammation	Headaches, rhinitis.
Optipranolol (Bausch & Lomb)	Metipranolol 0.3% solution	Nonselective beta-adrenergic blocker	IOP reduction	Worsens COPD and asthma, bradycardia, depression (rare).
Diamox (Bausch & Lomb)	Acetazolamide, 250 mg, or sequel, 500 mg	Oral carbonic anhydrase inhibitor	IOP reduction	Sulfonamide sensitivity, kidney disease (renal calculi), liver disease (cirrhosis), pulmonary disease, Stevens-Johnson syndrome, blood dyscrasias, paresthesias, digestive problems.
Timoptic (Merck) Betimol (Santen)	Timolol maleate, 0.5% solution	Nonselective beta-adrenergic blocker	IOP reduction	Worsens asthma and COPD, bradycardia, depression.
Neosporin (Monarch)	Neomycin and polymyxin b sulfate with gramicidin	Antimicrobial aminoglycoside (neomycin)	Bacterial conjunctivitis	Anaphylaxis
Cosopt (Merck)	Dorzolamide HCl and timolol-maleate	Carbonic anhydrase inhibitor with beta-blocker	IOP reduction	Worsens asthma and COPD, depression, bradycardia, sulfonamide-type hypersensitivity reactions, kidney failure.

Continued

DRUG BRAND NAME AND MANUFACTURER	GENERIC NAME	CLASSIFICATION	DESIRED EFFECT/ PURPOSE	SYSTEMIC SIDE EFFECTS
Trusopt (Merck)	Dorzolamide, 2.0% ophthalmic solution	Carbonic anhydrase inhibitor	IOP reduction	Blood dyscrasias, allergy/hypersensitivity to sulfonamides (rare), bronchospasm, fatigue, Stevens-Johnson syndrome, bitter taste.
Daranide (Merck)	Dichlorphenamide	Oral carbonic anhydrase inhibitor	IOP reduction	Renal failure, COPD, nausea.
Voltaren (Novartis Pharmaceuticals)	Diclofenac sodium solution, 0.1%	Nonsteroidal antiinflammatory drug	Inflammation reduction	Abdominal pain, headaches, vomiting.
Zaditor (Novartis)	Ketotifen fumarate 0.025%	Mast-cell stabilizer	Allergic conjunctivitis	Headaches, cold-like symptoms.
Xalatan (Pfizer)	Latanoprost, 0.005% solution.	Prostaglandin F2-alpha-analogue	IOP reduction	May worsen asthma, angina, flu-like symptoms, bradycardia, depression (all rare, safest class of all glaucoma medications).

IOP, Intraocular pressure; *COPD,* chronic obstructive pulmonary disease; *HDL,* high-density lipoprotein, *HCl,* hydrochloride.

APPENDIX 2

Ocular Manifestations of Systemic Medications

GENERIC NAME OR DRUG CLASS	BRAND NAME (EXAMPLE)	INDICATION	OCULAR SYMPTOMS	OCULAR SIGNS
Abacavir	Ziagen	HIV/AIDS	Sore eyes	Conjunctivitis, yellow conjunctiva
Acarbose	Precose	Type 2 diabetes		Yellow conjunctiva
ACE inhibitors	Accupril, Capoten, Lotensin	High blood pressure	Blurred vision with nicardipine	
Acetaminophen	Tylenol	Pain relief, fever reduction		Yellow conjunctiva
Acitretin	Soriatane	Psoriasis	Blurred vision, eye pain, photophobia	Loss of eyebrows, lid swelling, photophobia
Acyclovir	Zovirax	Herpes virus	Blurred vision	Red or yellow conjunctiva
Allopurinol	Aloprim	Gout		Red or yellow conjunctiva, optic neuritis, macular retinitis, iritis, conjunctivitis, amblyopia (?)
Amantadine	Symmetrel	Type A influenza	Blurred vision, photophobia, one case of bilateral sudden loss of vision (recovered after drug cessation)	Keratitis including corneal punctate subepithelial opacities or edema, "ocular nerve" palsy (!), mydriasis
Aminoglutethimide	Cytadren	Adrenal cortex		Yellow conjunctiva
Amiodarone	Cordarone	Arrhythmia	Blurred vision, haloes, photophobia, dry eyes, permanent blindness, diplopia	Whorl-like corneal epithelial opacities, anterior subcapsular opacities of the lens, pseudotumor cerebri with papill-edema, optic neuropathy, optic neuritis (?), nystagmus
Amlodipine	Norvasc	Angina		Yellow conjunctiva
Amphetamine	Dexedrine	ADHD	Blurred vision	
Amphotericin B	Amphocin	Fungal infection	Diplopia	
Anabolic steroid	Durabolin	Weight gain, anemia		Yellow conjunctiva
Androgens/ estrogens	Estratest/ Danazol	Menopause	Contact lens intolerance, diplopia	Yellow conjunctiva, conjunctival edema, cataracts
Anticholinergics	Bentyl	Cramps	Blurred vision, photophobia	Reduced accommodation

Continued

GENERIC NAME OR DRUG CLASS	BRAND NAME (EXAMPLE)	INDICATION	OCULAR SYMPTOMS	OCULAR SIGNS
Anticonvulsants	Dilantin	Epilepsy	Vision changes	Nystagmus
Antidepressants	MAO inhibitors such as Nardil	Mental depression	Photophobia, blurred vision	Dilated pupil
Antidepressants	Tricyclics like Elavil	Mental depression	Blurred vision, eye pain, photophobia	Mydriasis
Antidiabetic agents	Amaryl	Type 2 diabetes	Blurred vision	
Antidyskinetics	Cogentin	Parkinson's disease	Eye pain, visual blur	
Antihistamines	Allegra	Allergy	Contact lens intolerance, blurred vision	Dry eye, mydriasis
Antimyasthenics	Neostigmine	Myasthenia gravis	Blur, watery eyes	Miosis
Atorvastatin	Lipitor	Cholesterol regulation		Conjunctivitis, swollen eyelids
Baclofen	Lioresal	Multiple sclerosis	Blur, diplopia	Nystagmus, strabismus, miosis, mydriasis
Barbiturates	Nembutal	Anxiety	Blurred vision	Swollen eyelids, abnormal eye movements
Belladonna alkaloids	Donnatal	Cramps	Blurred vision, photophobia	Dry eyes, reduced accommodation, mydriasis
Beta-adrenergic blocking agents	Inderal	High blood pressure		Yellow conjunctiva
Botulinum toxin	Botox	Blepharospasm, strabismus		Dry eye, corneal irritation, ptosis
Carbamazepine	Tegretol	Epilepsy	Blur, diplopia	Nystagmus, yellow conjunctiva, oculomotor disturbance, scattered punctate, lens opacities
Carbonic anhydrase inhibitors	Diamox	Glaucoma	Photophobia	Increased accommodation, yellow conjunctiva
Cevimeline hydrochloride	Evoxac	Sjögren's syndrome	Itchy eyes, blur, vision loss, night vision problems	Corneal changes
Chloroquine	Aralen	Malaria	Blur, vision loss, halos, photophobia	Whorl-like epithelial opacities of the cornea, reduced accommodation, retinopathy (narrowing arterioles, optic disc pallor, optic atrophy, macular lesions)
Cisapride	Propulsid	Heartburn	Blur	
Citalopram	Celexa	Depression	Blur	
Clomiphene	Clomid	Fertility	Blur, flashes of light, diplopia, photophobia	Yellow conjunctiva, one case of posterior cortical cataract
Clonidine	Catapres	High blood pressure	Burning	Miosis
Corticosteroids	Nasonex nasal spray	Allergy		Glaucoma, cataract, reduced wound healing, exophthalmos
Decongestants	Sudafed	Allergy	Contact lens intolerance	Dry eye
Delavirdine	Rescriptor	HIV/AIDS	Blurred vision, diplopia, dry eyes, photophobia	Conjunctivitis, nystagmus

GENERIC NAME OR DRUG CLASS	BRAND NAME (EXAMPLE)	INDICATION	OCULAR SYMPTOMS	OCULAR SIGNS
Dexmethylphenidate (amphetamine cogener)	Focalin	ADHD, obesity	Blur	Accommodative changes, mydriasis
Difenoxin with atropine	Motofen	Diarrhea	Blur	Reduced accommodation
Digitalis	Lanoxin	Increases heart strength	Blur, yellow vision	
Disopyramide phosphate	Norpace	Abnormal heart rhythm	Blur	Dry eyes, contact lens intolerance
Disulfiram	Antabuse	Alcoholism	Blur, eye pain, dry eyes	Yellow conjunctiva, optic neuritis
Diuretics (loop)	Lasix, Furosemide	High blood pressure	Blur	Yellow vision with furosemide
Donepezil	Aricept	Alzheimer's		Sunken-appearing eyes, conjunctivitis
Doxepin	Zonalon, Sinequan	Eczema	Blur	Mydriasis
Enalapril maleate	Enalapril	High blood pressure (ACE inhibitor)	Dry eyes	Yellow conjunctiva
Encainide	Enkaid	Antiarrhythmic	Blur, diplopia	Periorbital edema
Epoetin	Epogen, Procrit	Antianemia	Visual disturbances	Conjunctivitis
Ergoloid mesylates	Gerimal	Mood behavior	Blur	
Estrogens	Premarin, clomiphene	Menopause, osteoporosis, breast cancer	Change or loss of vision (rare), diplopia	
Etanercept	Enbrel	Rheumatoid arthritis	Blur	Blue-yellow color blindness, optic neuritis, uveitis
Ethambutol	Myambutol	Tuberculosis	Blur, eye pain, loss of vision	Red-green color blindness, optic neuritis, visual field loss
Ethchlorvynol	Placidyl	Insomnia	Diplopia, blur	Yellow conjunctiva
Felbamate	Felbatol	Seizure control in epilepsy	Blurred vision, diplopia	Miosis, visual field defect
Fentanyl	Actiq	Narcotic analgesic to reduce pain	Vision change	
Flecainide	Tambocor	Antiarrhythmics	Blurred vision, photophobia, diplopia	Yellow conjunctiva, "spots" in vision, nystagmus, decreased accommodation
Fludarabine	Fludara	Antimetabolite to treat chronic lymphocytic leukemia	Blindness	Yellow conjunctiva, visual disturbances
Fludrocortisone	Florinef	Corticosteroid	Blindness, blurred vision	Proptosis, yellow conjunctiva, posterior subcapsular cataract, exophthalmos, increased intraocular pressure
Fluoroquinolones	Cipro	Antibiotic	Blurred vision	Yellow conjunctiva
Fluticasone	Flovent	Corticosteroid inhaler for asthma	Blindness, blurred vision, eye pain	Conjunctivitis
Gabapentin	Neurontin	Seizure control in epilepsy	Diplopia, blurred vision, pain, photophobia	Nystagmus, cataract, conjunctivitis, dry eyes, visual field defect, ptosis

Continued

GENERIC NAME OR DRUG CLASS	BRAND NAME (EXAMPLE)	INDICATION	OCULAR SYMPTOMS	OCULAR SIGNS
Guanabenz	Wytensin	Antihypertensives		Miosis
Haloperidol	Haldol	Mental conditions	Blurred vision	Unexplained reduced visual acuity, cataracts, retinopathy, fixed stare
Hydrocodone	Vicoprofen	Pain relief	Blurred vision	
Hydroxychloroquine	Plaquenil	Antiprotozoals (malarial prevention), antirheumatoid arthritis, lupus erythematosus	Blurred vision	Pigmentation of corneal endothelium and Descemet's membrane, reduced accommodation, retinopathy, optic nerve pallor, macular lesions
Inamrinone	Inamrinone	Heart failure		Yellow conjunctiva
Infliximab	Remicade	Crohn's disease and rheumatoid arthritis		Yellow conjunctiva, optic neuritis
Isoniazid	Laniazid	Tuberculosis	Blurred vision	Yellow conjunctiva, optic neuritis, optic atrophy
Isotretinoin	Accutane	Acne, psoriasis	Blurred vision, reduced night vision, dry eye, diplopia	Conjunctivitis, corneal opacities and neovascularization, cataracts, color vision alteration
Ketorolac tromethamine	Toradol	Pain relief	Blurred vision	
Lamotrigine	Lamictal	Seizure control in epilepsy	Blurred vision, diplopia, photophobia	Nystagmus, strabismus, ptosis
Leflunomide	Arava	Rheumatoid arthritis	Blurred vision	Yellow conjunctiva, cataract, conjunctivitis
Levodopa	Sinemet	Parkinson's disease	Blurred vision, diplopia, eyelid spasms	Mydriasis, ophthalmoplegia, miosis, lid retraction
Lithium	Lithobid	Bipolar disorder	Blurred vision	Pseudotumor cerebri, papilledema
Maprotiline hydrochloride	Ludiomil	Mental depression	Blurred vision	
Mecamylamine	Inversine	Antihypertensive	Blurred vision	Mydriasis
Meclizine	Antivert	Motion sickness and vertigo	Blurred vision, diplopia	
Metformin	Glucophage	Type 2 diabetes	Blurred vision	
Methotrexate		Antimetabolite for cancer, psoriasis, rheumatoid arthritis	Blurred vision	Yellow conjunctiva, conjunctivitis
Methyldopa	Aldomet	Antihypertensive	Blurred vision	Yellow conjunctiva
Methysergide maleate	Sansert	Migraine	Vision changes	
Midodrine	ProAmatine	Treats low blood pressure	Blurred vision (common)	
Minoxidil topical	Rogaine	Scalp hair growth	Blurred vision	Conjunctivitis
Modafinil	Provigil	Narcolepsy	Blurred vision	
Molindone	Moban	Mental depression	Blurred vision	Ophthalmoplegia
Moricizine	Ethmozine	Antiarrhythmic	Blurred vision	
Naratriptan	Amerge	Migraine	Blurred vision	
Narcotic analgesics with acetaminophen	Tylenol with codeine	Pain relief	Blurred vision, diplopia	Miosis, yellow conjunctiva

GENERIC NAME OR DRUG CLASS	BRAND NAME (EXAMPLE)	INDICATION	OCULAR SYMPTOMS	OCULAR SIGNS
Nateglinide	Starlix	Type 2 diabetes	Blurred vision	
Nefazodone hydrochloride	Serzone	Mental depression	Blurred vision, eye pain, diplopia	Mydriasis
Nevirapine	Viramune	HIV/AIDS		Injected conjunctiva, yellow conjunctiva
Niacin (vitamin B_3)	Niacor	Nutrition supplementation		Yellow conjunctiva
Nitrates	Nitrolingual	Angina	Blurred vision	
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Voltaren, Indomethacin	Arthritis, analgesia, antipyretic	Photophobia	Eyelid swelling, corneal toxicity with keratopathy
Octreotide	Sandostatin	Severe diarrhea	Blurred vision	Bell's palsy
Olanzapine	Zyprexa	Psychosis	Diplopia	
Olmesartan medoxomil	Benicar	Antihypertensive	Blurred vision, eye pain	
Olsalazine	Dipentum	Ulcerative colitis		Yellow conjunctiva
Omeprazole	Prilosec	GERD, gastric ulcers	Blurred vision	
Oxcarbazepine	Trileptal	Epilepsy	Change in vision, diplopia, blurred vision	
Pantoprazole sodium	Protonix	GERD	Sudden loss of vision, blurred vision	Lid swelling, yellow conjunctiva
Paroxetine hydrochloride	Paxil	Mental depression, panic disorder, anxiety disorder	Blurred vision	Ophthalmoplegia, mydriasis
Pergolide mesylate	Permax	Parkinson's disease	Blurred vision, temporary blindness, diplopia	Reduced accommodation, conjunctivitis, ocular pain, mydriasis, keratitis, cataract, glaucoma
Phenothiazines (chlorpromazine)	Thorazine, Mellaril, Stelazine, Chlorpromazine	Mental and emotional disorders	Changes in color vision, night blindness	Ophthalmoplegia, pigmentation of corneal endothelium and Descemet's membrane, anterior subcapsular (stellate-shaped) cataract, scleral discoloration, pigmented retinopathy
Phenoxybenzamine	Dibenzyline	Antihypertensive		Miosis
Primidone	Mysoline	Anticonvulsant	Diplopia	Nystagmus, eyelid edema
Propafenone hydrochloride	Rythmol	Antiarrhythmic	Blurred vision	
Quinine sulfate	Quinine	Malaria	Blurred vision, diplopia, photophobia, night blindness	Distorted color vision, optic atrophy
Raloxifene hydrochloride	Evista	Osteoporosis in postmenopausal women	Loss of vision	
Rifampicin	Rifadin	Tuberculosis	Visual disturbances	Yellow conjunctiva, injected conjunctiva
Rizatriptan benzoate	Maxalt	Migraine	Blurred vision, dry eyes with irritation	Toxicity of melanin-rich ocular tissues (potential)
Salicylates	Anacin, aspirin, Ecotrin	Pain relief and fever reduction		Eyelid swelling

Continued

GENERIC NAME OR DRUG CLASS	BRAND NAME (EXAMPLE)	INDICATION	OCULAR SYMPTOMS	OCULAR SIGNS
Sertraline hydrochloride	Zoloft	Mental depression	Blurred vision, diplopia	Mydriasis, reduced accommodation, conjunctivitis, ocular pain, anisocoria, exophthalmos, hyphema, optic neuritis
Sildenafil citrate	Viagra	Erectile dysfunction	Abnormal vision, blurred vision, color vision changes, photophobia, diplopia, vision loss	Mydriasis, blue-green vision, conjunctivitis, cataract, dry eyes, blindness secondary to anterior ischemic optic neuropathy
Sumatriptan	Imitrex	Migraine	Vision changes	Swollen eyelids, lacrimation, reduced accommodation, conjunctivitis, extraocular muscle disorder, keratitis, miosis, low vision, mydriasis, retinal vein and artery occlusions, ischemic optic neuropathy
Tamoxifen citrate	Nolvadex	Breast cancer treatment in women and men	Blurred vision	Yellow conjunctiva, cataract development, crystal deposit in retinal blood vessels, color vision changes, optic neuritis, retinal vein occlusion
Terazosin hydrochloride	Hytrin	Antihypertensive	Blurred vision	Conjunctivitis
Terbinafine hydrochloride	Lamisil	Antifungal		Yellow conjunctiva
Tolterodine tartrate	Detrol	Bladder problems	Blurred vision	Reduced facility of accommodation, xerophthalmia
Topiramate	Topamax	Epilepsy	Vision problems, blurred vision, diplopia, eye pain, vision loss	Nystagmus, superciliary effusions leading to shallow anterior chamber with angle-closure glaucoma and sudden myopia (caused by forward displacement of lens from effusions)
Venlafaxine	Effexor	Mental depression	Vision changes, blurred vision	
Zaleplon	Sonata	CNS depressant	Blurred vision, diplopia	
Zolmitriptan	Zomig	Migraine		Swollen eyelids, potential toxicity from accumulations within melanin-rich ocular tissues
Zolpidem tartrate	Ambien	Insomnia	Diplopia, abnormal vision	Eye irritation, ocular pain, scleritis, reduced accommodation, corneal ulcers, glaucoma

ACE, Angiotensin-converting enzyme; *MAO,* monoamine oxidase; *GERD,* gastroesophageal reflux disease; *ADHD,* attention deficit hyperactivity disorder, *CNS,* central nervous system.

APPENDIX 3

Injection Techniques Specifically Tailored for the Optometrist

Bruce Muchnick and Janice Glass

Injectable drugs can be administered in several ways. The two routes that are emphasized here are the subcutaneous (SQ) route and the intramuscular (IM) route. The time for an injectable medication to take effect can vary from seconds to longer than 30 minutes depending on the purposeful choice of the drug, dosage, and route of administration. Although this control is a distinct advantage of the parenteral technique, injections are the most hazardous way to administer a drug. Exercising caution and maintaining proper technique prevent infection and avoid damage to the patient's nerves, blood vessels, tissues, and bones.

Note: Injections are potentially dangerous techniques that should be attempted by the optometrist only after he or she has received advanced training and appropriate certification.

THE SUBCUTANEOUS ROUTE

Use

The SQ route is used to deliver a dose of epinephrine to mitigate an allergic reaction; epinephrine is effective in this instance when given by the SQ route. Because of its high potency, epinephrine given IM could cause life-threatening arrhythmias and hypertension.

Contraindications

To prevent damage to subcutaneous tissue, drugs that are irritating, oil-based, or concentrated are given by the IM route. Administration of one of these solutions by the SQ route could cause tissue extravasation, necrosis, abscess, or tissue ischemia.

Subcutaneous Sites

An injection into SQ tissue is usually best done at a site where no blood vessels, bones, or nerve endings are present near the surface. Frequently used sites are the thighs, the hips, the fat pad of the lower abdomen, and the flabby tissue above the elbow of the upper arm, (Figures Al to A4).

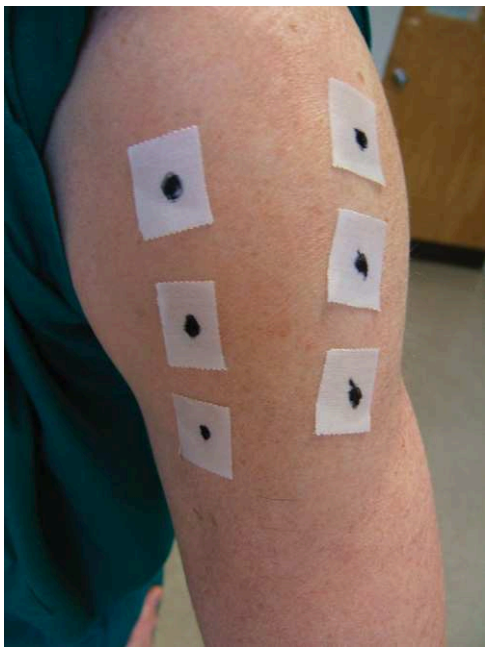


FIGURE A1 ■ Flabby tissue above the elbow of the upper arm is a frequently used site for a subcutaneous injection.

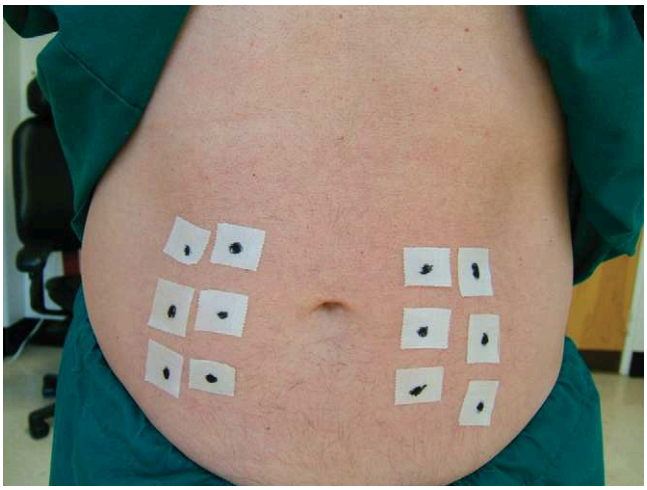


FIGURE A2 ■ Twelve SQ sites are found around the fat pad in the lower abdomen of this elderly patient.

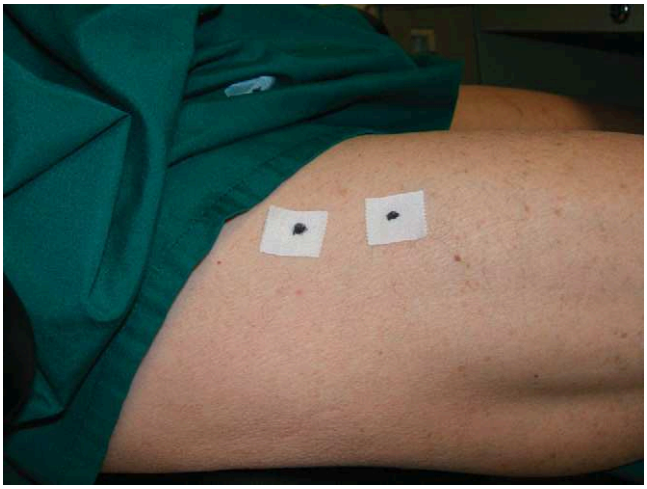


FIGURE A4 ■ The upper thigh is a commonly used SQ site.

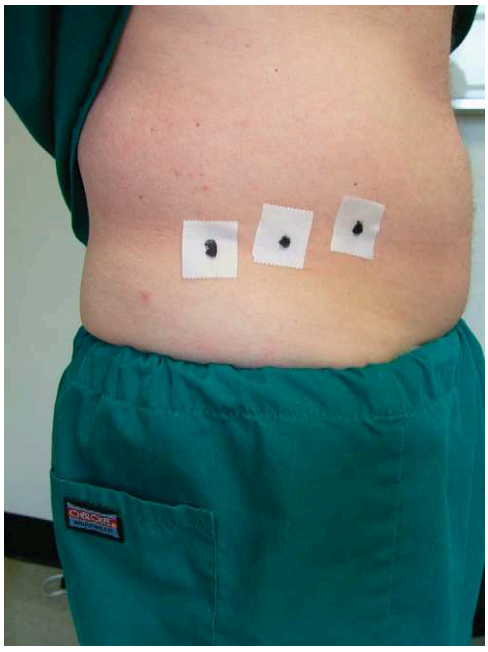


FIGURE A3 ■ Three sites around each hip are appropriate SQ sites where no significant blood vessels, bones, or nerve endings are present.

Subcutaneous Needle

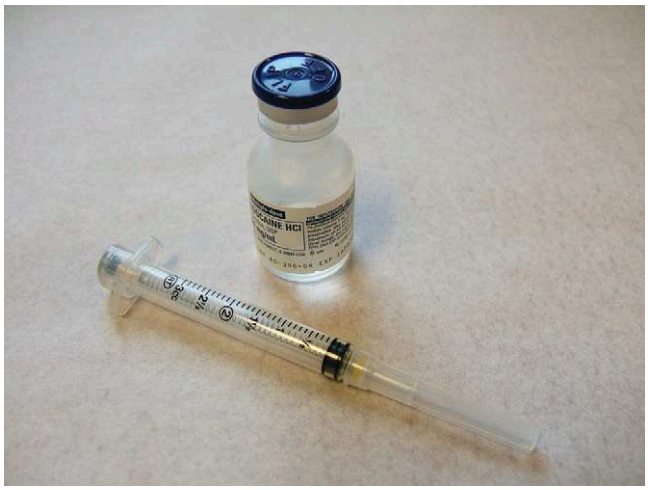
The optometrist should choose a 25- to 27-gauge, $\frac{5}{8}$-inch needle with a 3-ml syringe or a tuberculin syringe. The volume range for SQ injections is 0.1 ml to 1.0 ml.

Onset and Duration of Action

Onset is in minutes (as in the case of epinephrine) to hours (as in some types of insulin and heparin). The duration of action is hours to weeks.

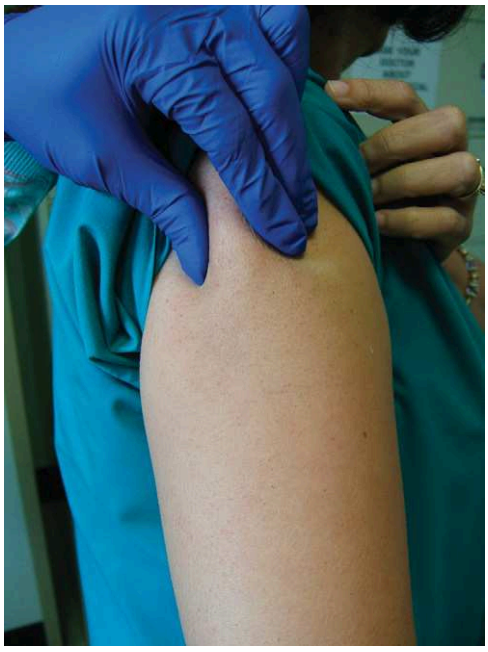
Administration by Subcutaneous Injection

Step 1: Obtain equipment and medication. Assemble syringe and needle according to manufacturer's instructions if necessary. Today, most such instruments are preassembled and sterilized.

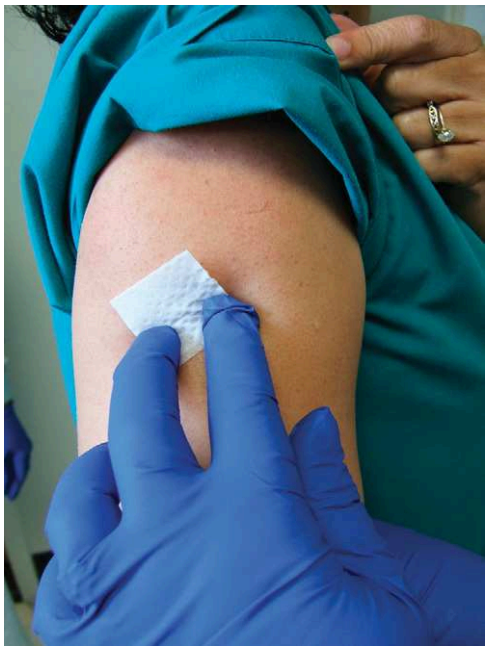


Step 2: Withdraw the drug by inverting the vial and pulling back on the plunger to the desired dose at eye level. Withdraw needle from vial and depress plunger to remove air from barrel.

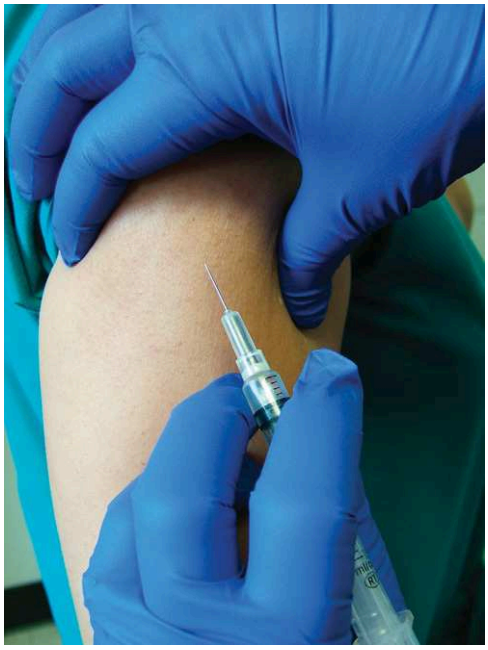
Step 3: Select the site. Pinch at least a 1-inch fat fold. Select whatever angle permits the needle to reach the tissue between the muscle and the fat.



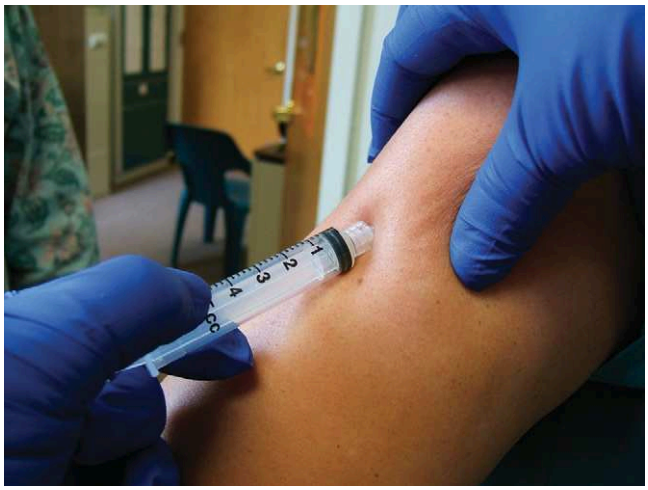
Step 4: Cleanse the skin area in a circular, outward motion with an alcohol swab and let it air dry.



Step 5: Insert the needle quickly with a dart-like motion (it is not necessary to aspirate) at a 45- to 90-degree angle.



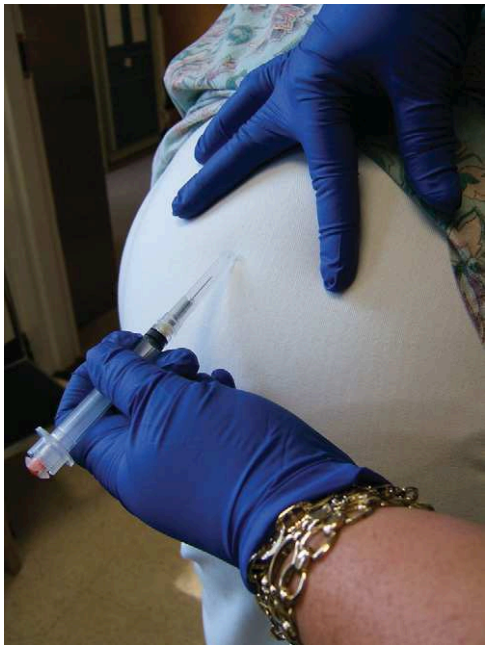
Step 6: Inject the drug slowly and withdraw the needle. If bleeding is present, apply gentle pressure with a dry, sterile sponge. Do not massage the site.



THE INTRAMUSCULAR ROUTE

The IM route is used when one is delivering a larger volume of drug than with the SQ route, when giving an irritating drug, or when a more rapid onset is needed. Absorption into the bloodstream is faster than with the SQ route because of the greater blood supply to the muscles.

Complications from IM injections include necrosis, skin sloughing, abscesses, nerve injury, and persistent pain. To safely administer an IM injection, the site chosen should not be near large blood vessels and large nerves.



Intramuscular Sites

The ventrogluteal (gluteus medius and minimus) site has dense muscles and no major blood vessels or nerves.

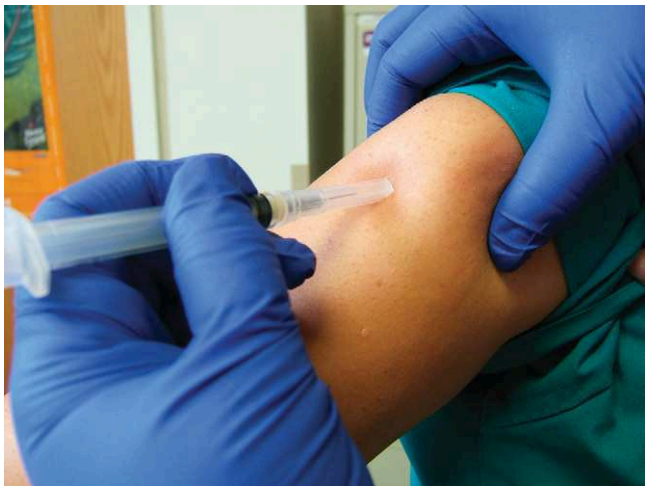
The dorsogluteal (gluteus maximus) site is the most dangerous. An injection made too close to the buttocks crease could puncture the superior gluteal artery and damage the sciatic nerve permanently. This area is a common site of injection, however. To locate the proper area, one can picture a cross, superimposed on the right gluteus maximus with the intersection of the horizontal and vertical lines located in the center of the right cheek. The only safe area for an IM injection in the dorsogluteal site is in the superior lateral box formed by the cross (Figure A5).

The vastus lateralis (outer midthigh) site has no major arteries or blood vessels. This area is easily located but can be painful because of the large number of nerve endings in the muscle. It is often used in children (Figure A6).

The deltoid site is easily accessible but is a small muscle; therefore no more than 2 ml of medication can be given in one injection. The optometrist can give as much as 2 ml of medication in each arm if necessary (Figure A7).

The Needle

Choose a 22- to 25-gauge, 1.5-inch needle for the deltoid. Choose a 20- to 23-gauge, 1.5- to 3-inch needle for the dorsogluteal, ventrogluteal, and vastus lateralis sites. For children, use the vastus lateralis site with a 23- to 26-gauge, 1.5-inch needle.

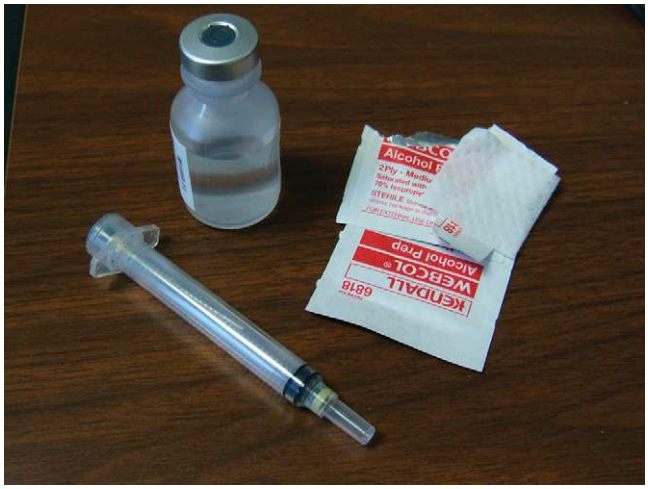


Onset and Duration of Action

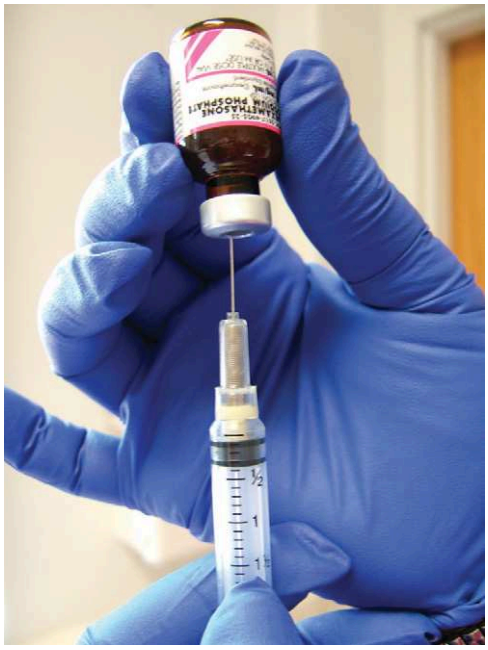
Onset is less than 1 hour, and the duration is hours to weeks.

Administration by Intramuscular Route

Step 1: Obtain equipment and medication.

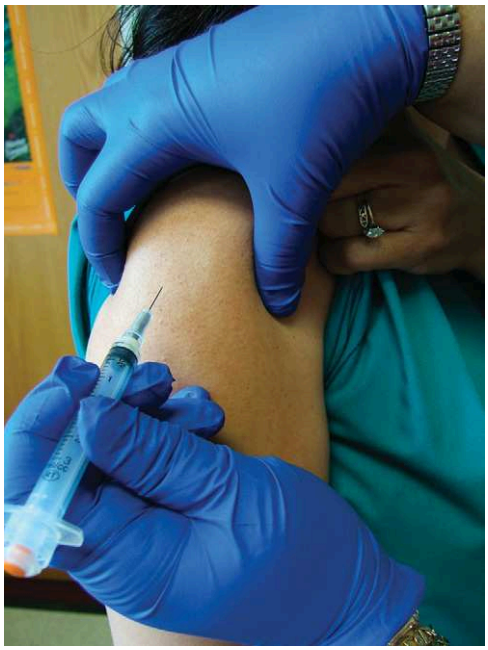


Step 2: The optometrist should withdraw the drug by inverting the vial and injecting a small amount of air into the vial. Pull back on the plunger to the desired dose at eye level. If breaking an ampule, first flick the solution into the bottom. Using an alcohol swab or 2 x 2-inch gauze pad, break the ampule at the neck, and withdraw the medication.

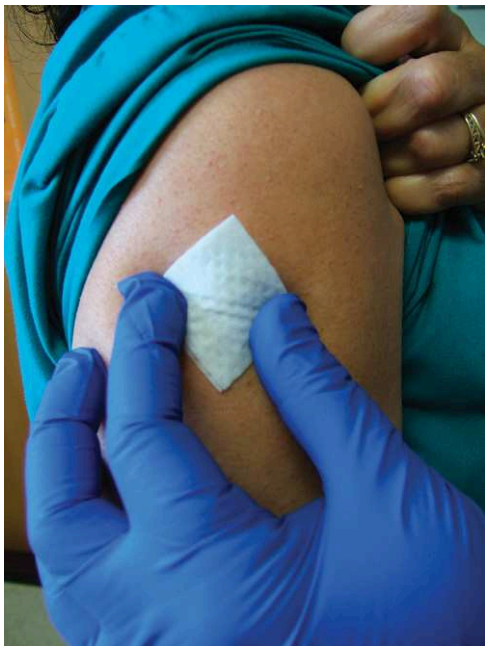


Step 3: Select the site. Cleanse the site in a circular outward motion with an alcohol swab; let dry. With the nondominant hand, stretch the skin taut with the thumb and index finger.

Step 4: With the dominant hand, insert the needle quickly at a 90-degree angle with a dart-like motion. Aspirate the plunger by pulling back on its handle. If blood is present, withdraw the syringe and start again because a blood vessel has been entered. If no blood is present, inject the medication. Then slowly withdraw the needle at the same angle it was inserted.



Step 5: Apply pressure with a sterile sponge. Massaging the site is not necessary.



Step 6: Dispose of all needles in a proper container.

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