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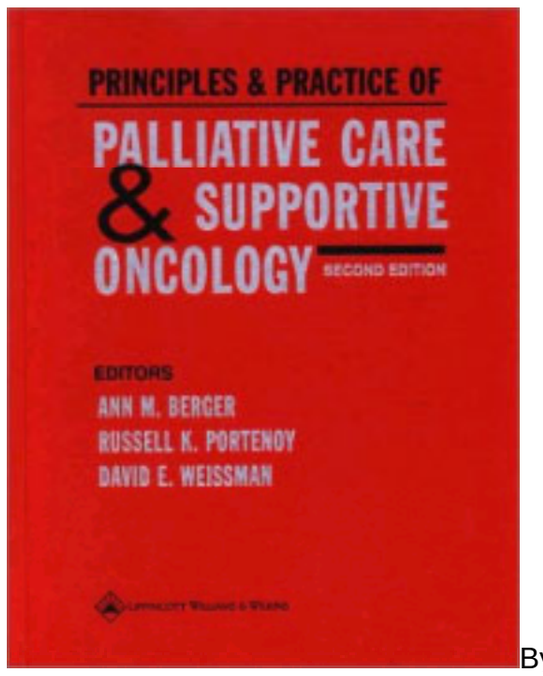

By OkDoKeY

Principles and Practice of Palliative Care and Supportive Oncology

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To our spouses and children, whose love and support make our work possible
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FOREWORD

A folk saying dating to the fifteenth century calls the duty of a physician “to cure sometimes, to relieve often, to comfort always.” The modern oncologist has the tools to cure approximately 50% of all individuals who develop cancer, although virtually every cancer patient sometime during the course of the disease and treatment has the need for relief from symptoms and comfort from anxieties. The physical symptoms associated with cancer and its treatment, as well as the emotional burdens on patients and their families, profoundly impact the quality of life of cancer patients.

The scope of information in modern oncology ranges from understanding the single nucleotide base changes in oncogenes that can result in malignant transformation to understanding the emotional needs of a patient with metastatic cancer in the last hours of life. The practicing oncologist faces the daunting challenge of translating a vast array of new clinical and scientific information to benefit the care of individual cancer patients.

Most modern textbooks of oncology as well as the majority of articles in peer-reviewed journals deal predominantly with the pathogenesis of disease and attempts to develop curative treatments. Coordinated information dealing with the supportive aspects of cancer care designed to relieve symptoms and to comfort anxieties has often been difficult to find. Only recently have major institutions organized separate services concentrating on cancer care staffed by health care professionals whose training is concentrated on the palliative and supportive care needs of cancer patients.

The information needed by all health care providers to “relieve often, to comfort always” all cancer patients, whether curable or not, is found in these pages of the comprehensive second edition of *Principles and Practice of Palliative Care and Supportive Oncology*. The editors have provided a comprehensive guide to dealing with the severe physical and emotional impact of the cancer itself, as well as the side effects of the treatments administered.

The contents of this text provide the practicing oncologist with the base of information needed to deal with this extraordinarily important aspect of modern oncology.

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PREFACE FROM THE FIRST EDITION

The term *supportive oncology* refers to those aspects of medical care concerned with the physical, psychosocial, and spiritual issues faced by persons with cancer, their families, their communities, and their health care providers. In this context, supportive oncology describes both those interventions used to support patients who experience adverse effects caused by antineoplastic therapies and those interventions now considered under the broad rubric of palliative care. The term *palliative* is derived from the Latin *pallium*: to cloak or cover. At its core, palliative care is concerned with providing the maximum quality of life to the patient-family unit.

In 1990, the World Health Organization (WHO) published a landmark document, *Cancer Pain Relief and Palliative Care*, which clearly defined the international barriers and needs for improved pain and symptom control in the cancer patient.

The WHO definition of palliative care is (1)

> The active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social, and spiritual problems is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families. Many aspects of palliative care are also applicable earlier in the course of the illness in conjunction with anti-cancer treatment.

In 1995, the Canadian Palliative Care Association chose a somewhat broader definition that emphasizes a more expanded role of palliative care (2):

> Palliative care, as a philosophy of care, is the combination of active and compassionate therapies intended to comfort and support individuals and families who are living with a life-threatening illness. During periods of illness and bereavement, palliative care strives to meet physical, psychological, social, and spiritual expectations and needs, while remaining sensitive to personal, cultural, and religious values, beliefs, and practices. Palliative care may be combined with therapies aimed at reducing or curing the illness, or it may be the total focus of care.

In developing this textbook, the editors have brought together those elements of palliative care that are most applicable to the health care professional caring for cancer patients, and have combined this perspective with a detailed description of related therapies used to support patients in active treatment. The editors view these interventions as a necessary and vital aspect of medical care for all cancer patients, from the time of diagnosis until death. Indeed, most patients will have a significant physical symptom requiring treatment at the time of their cancer diagnosis.

Even when cancer can be effectively treated and a cure or life prolongation is achieved, there are always physical, psychosocial, or spiritual concerns that must be addressed to maintain function and optimize the quality of life. For patients whose cancer cannot be effectively treated, palliative care must be the dominant mode, and one must focus intensively on the control of distressing symptoms. Planning for the end of life and ensuring that death occurs with a minimum of suffering and in a manner consistent with the values and desires of the patient and family are fundamental elements of this care. Palliative care, as a desired approach to comprehensive cancer care, is appropriate for all health care settings, including the clinic, acute care hospital, long-term care facility, or home hospice.

Palliative care and the broader concept of supportive care involve the collaborative efforts of an interdisciplinary team. This team must include the cancer patient and his or her family, care givers, and involved health care providers. Integral to effective palliative care is the opportunity and support necessary for both care givers and health care providers to work through their own emotions related to the care they are providing.

In organizing this textbook, the editors have recognized the important contributions of medical research and clinical care that have emerged from the disciplines of hospice and palliative medicine; medical, radiation, and surgical oncology; nursing; neurology and neuro-oncology; anesthesiology; psychiatry and psychology; pharmacology; and many others. The text includes chapters focusing on the common physical symptoms experienced by the cancer patient; a review of specific supportive treatment modalities, such as blood products, nutritional support, hydration, palliative chemotherapy, radiotherapy, and surgery; and, finally, a review of more specialized topics, including survivorship issues, medical ethics, spiritual care, quality of life, and supportive care in elderly, pediatric, and AIDS patients.

There are many promising new cancer treatments on the horizon. No matter what these new treatments will offer in terms of curing the disease or prolonging life, cancer will remain a devastating illness, not only for the affected patients, but for their families, community, and health care providers. Providing excellent, supportive care will continue to be a goal for all health care providers.

The authors would like to thank our many contributors for their efforts. We are also grateful to our publisher and secretaries, whose oversight and gentle prodding were essential to our success. Finally, we want to express our gratitude to our families and colleagues, who accommodated our needs in bringing the volume to fruition and provided the support we needed throughout the process.

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PREFACE

> You matter because you are you. You matter to the last moment of your life, and we will do all that we can not only to help you die peacefully, but also to live until you die.
>
> —Dame Cicely Saunders

We offer this second edition as a contribution to the changes that have taken place in palliative medicine in the past 4 years. Palliative medicine is an art and a science of patient-focused, family-oriented, relationship-centered care, from the onset of a serious life-challenging illness throughout the trajectory of illness, aimed at enhancing quality of life and minimizing suffering.

Clearly, palliative care has developed into a recognized discipline. In the United States, palliative care is rapidly evolving in parallel with a well-established hospice model. The U.S. version of hospice remains a critically important part of this broader approach to palliative care, which attempts to help patients and their families deal with quality-of-life issues throughout the trajectory of illness, even when treatment has curative intent.

In this second edition, we have added several new chapters, including hiccups, physiatric approaches, bone pain, management of hypercoagulable states and coagulopathy, management of advanced heart failure, cross-cultural issues, models of palliative care, ethics and the law, music and art therapy, and complementary and alternative approaches.

As before, when we edited our first edition, there are many new medical treatments on the horizon that cure disease. But equally important is providing excellent palliative care aimed at relieving suffering.

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1

CANCER PAIN: PRINCIPLES OF ASSESSMENT AND SYNDROMES

NATHAN I. CHERNY

Surveys indicate that pain is experienced by 30–60% of cancer patients during active therapy and more than two-thirds of those with advanced disease (1). This has been corroborated in a series of recent studies which identified a pain prevalence of 28% among patients with newly diagnosed cancer (2), 50–70% among patients receiving active anticancer therapy (3,4), and 64–80% among patients with far advanced disease (5,6,7 and 8). Unrelieved pain is incapacitating. It precludes a satisfying quality of life. It interferes with physical functioning and social interaction. It is strongly associated with heightened psychological distress (9,10). Persistent pain interferes with the ability to eat (11), sleep (12,13), think, interact with others (10,14), and is correlated with fatigue in cancer patients (15).

The relationship between pain and psychological well-being is complex and reciprocal. Mood disturbance and beliefs about the meaning of pain in relation to illness can exacerbate perceived pain intensity. The presence of pain is a major determinant of function and mood. The affective dimension of pain includes sensations of unpleasantness and emotions associated with future implications. The affective component of the pain experience is related to a central network of brain structures, including spinal pathways to limbic structures and medial thalamic nuclei, spinal pathways to somatosensory thalamic, and a cortico-limbic pathway to cortical areas. This cortico-limbic pathway integrates nociceptive input with contextual information and memory to provide cognitive mediation of pain affect (16).

The presence of pain can provoke or exacerbate existential distress (17), disturb normal processes of coping and adjustment (18,19 and 20), and augment a sense of vulnerability, contributing to a preoccupation with the potential for catastrophic outcomes (10,18).

The high prevalence of acute and chronic pain among cancer patients and the profound psychological and physical burdens engendered by this symptom oblige all treating clinicians to be skilled in pain management (21). Relief of pain in cancer patients is an ethical imperative. It is incumbent on clinicians to maximize the knowledge, skill, and diligence needed to attend to this task.

The undertreatment of cancer pain, which continues to be common (22,23), has many causes, among the most important of which is inadequate assessment (24,25). In a study to evaluate the correlation between patient and clinician evaluation of pain severity, Grossman et al. (25) found that when patients rated their pain as moderate to severe, oncology fellows failed to appreciate the severity of the problem in 73% of cases. In studies of pain relief among cancer patients in the United States (26) and in France (27), the discrepancy between patient and physician evaluation of the severity of the pain problem was a major predictor of inadequate relief. Surveys indicate that oncology clinicians recognize that suboptimal assessment is one of the most important causes of inadequate pain relief in cancer patients (24,28,29).

APPROACH TO CANCER PAIN ASSESSMENT

Assessment is an ongoing and dynamic process that includes evaluation of presenting problems, elucidation of pain syndromes and pathophysiology, and formulation of a comprehensive plan for continuing care. The objectives of cancer pain assessment include (a) the accurate characterization of the pain, including the pain syndrome and inferred pathophysiology, and (b) the evaluation of the impact of the pain and the role it plays in the overall suffering of the patient.

This assessment is predicated on the establishment of a trusting relationship with the patient in which the clinician emphasizes the relief of pain and suffering as central to the goal of therapy, and encourages open communication about symptoms. Clinicians should not be cavalier about the potential for symptom underreporting. Symptoms are frequently described as complaints and there is a common perception that the “good patient” refrains from complaining (30). The prevalence of pain is so great that an open-ended question about the presence of pain should be included at each patient visit in routine oncological practice. If the patient is either unable or unwilling to describe the pain, a family member may need to be questioned to assess the distress or disability of the patient.

Pain Syndromes

Cancer pain syndromes are defined by the association of particular pain characteristics and physical signs with specific consequences of the underlying disease or its treatment. Syndromes are associated with distinct etiologies and pathophysiologies, and have important prognostic and therapeutic implications. Pain syndromes associated with cancer can be either acute (Table 1-1) or chronic (Table 1-2). Whereas acute pains experienced by cancer patients are usually related to diagnostic and therapeutic interventions, chronic pains are most commonly caused by direct tumor effects. Adverse consequences of cancer therapy, including surgery, chemotherapy, and radiation therapy, account for 15–25% of chronic cancer pain problems. A small proportion of the chronic pains experienced by cancer patients are caused by pathology unrelated to either the cancer or the cancer therapy.

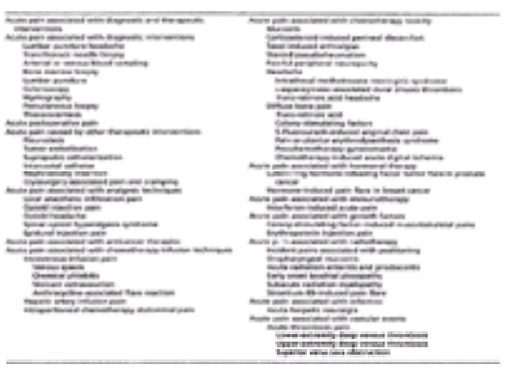

TABLE 1-1. CANCER-RELATED ACUTE PAIN SYNDROMES

TABLE 1-2. CANCER-RELATED CHRONIC PAIN SYNDROMES

Pain Characteristics

The evaluation of pain characteristics provides some of the data essential for syndrome identification. These characteristics include intensity, quality, distribution, and temporal relationships.

Intensity

The evaluation of pain intensity is pivotal to therapeutic decision-making (31,32). It indicates the urgency with which relief is needed and influences the selection of analgesic drug, route of administration, and rate of dose titration (31). Furthermore, the assessment of pain intensity may help characterize the pain mechanism and underlying syndrome. For example, the pain associated with radiation-induced nerve injury is rarely severe; the occurrence of severe pain in a previously irradiated region therefore suggests the existence of recurrent neoplasm or a radiation-induced second primary neoplasm.

Quality

The quality of the pain often suggests its pathophysiology. Somatic nociceptive pains are usually well localized and described as sharp, aching, throbbing, or pressurelike. Visceral nociceptive pains are generally diffuse and may be gnawing or crampy when due to obstruction of a hollow viscus, or aching, sharp, or throbbing when due to involvement of organ capsules or mesentery. Neuropathic pains may be described as burning, tingling, or shocklike (lancinating).

Distribution

Patients with cancer pain commonly experience pain at more than one site (3,4,33). The distinction between focal, multifocal, and generalized pain may be important in the selection of therapy, such as nerve blocks, radiotherapy, or surgical approaches. The term *focal pain*, which is used to denote a single site, has also been used to depict pain that is experienced in the region of the underlying lesion. Focal pains can be distinguished from those that are referred to a site remote from the lesion. Familiarity with pain referral patterns is essential to target appropriate diagnostic and therapeutic maneuvers (34,35) (Table 1-3). For example, a patient who develops progressive shoulder pain and has no evidence of focal pathology needs to undergo evaluation of the region above and below the diaphragm to exclude the possibility of referred pain from diaphragmatic irritation.

Pain mechanism	Site of lesion	Referral site
Visceral	Diaphragmatic irritation	Shoulder
	Urothelial tract	Inguinal region and genitalia
Somatic	C7-T1 vertebrae	Interscapular
	L1-2	Sacroiliac joint and hip
	Hip joint	Knee
	Pharynx	Ipsilateral ear
Neuropathic	Nerve or plexus	Anywhere in the distribution of a peripheral nerve
	Nerve root	Anywhere in the corresponding dermatome
	Central nervous system	Anywhere in the region of the body innervated by the damaged structure

TABLE 1-3. COMMON PATTERNS OF PAIN REFERRAL

Temporal Relationships

Cancer-related pain may be acute or chronic. Acute pain is defined by a recent onset and a natural history characterized by transience. The pain is often associated with overt pain behaviors (such as moaning, grimacing, and splinting), anxiety, or signs of generalized sympathetic hyperactivity, including diaphoresis, hypertension, and tachycardia. Chronic pain has been defined by persistence for 3 months or more beyond the usual course of an acute illness or injury, a pattern of recurrence at intervals over months or years, or by association with a chronic pathological process (1). Chronic, tumor-related pain is usually insidious in onset, often increases progressively with tumor growth, and may regress with tumor shrinkage. Overt pain behaviors and sympathetic hyperactivity are often absent, and the pain may be associated with affective disturbances (anxiety and/or depression) and vegetative symptoms, such as asthenia, anorexia, and sleep disturbance (36).

Transitory exacerbations of severe pain, over a baseline of moderate pain, may be described as “breakthrough pain” (37). Breakthrough pains are common in both acute or chronic pain states. These exacerbations may be precipitated by volitional actions of the patient (so-called incident pains), such as movement, micturition, cough or defecation, or by nonvolitional events such as bowel distention. Spontaneous fluctuations in pain intensity can also occur without an identifiable precipitant.

Inferred Pain Mechanisms

Inferences about the mechanisms that may be responsible for the pain are helpful in the evaluation of the pain syndrome and in the management of cancer pain. The assessment process usually provides the clinical data necessary to infer a predominant pathophysiology.

Nociceptive Pain

Nociceptive pain describes pain that is perceived to be commensurate with tissue damage associated with an identifiable somatic or visceral lesion. The persistence of pain is thought to be related to ongoing activation of nociceptors. Nociceptive pain that originates from somatic structures (somatic pain) is usually well localized and described as sharp, aching, burning, or throbbing. As previously described, pain that arises from visceral structures (visceral pain) is generally diffuse; pain characteristics may differ depending on the involved structures. From the clinical perspective, nociceptive pains (particularly somatic pains) usually respond to opioid analgesics (38,39 and 40) or to interventions that ameliorate or denervate the peripheral lesion.

Neuropathic Pain

The term *neuropathic pain* is applied when pain is due to injury to, or diseases of, the peripheral or central neural structures or is perceived to be sustained by aberrant somatosensory processing at these sites (41). It is most strongly suggested when a dysesthesia occurs in a region of motor, sensory, or autonomic dysfunction that is attributable to a discrete neurological lesion. The diagnosis can be challenging, however, and is often inferred solely from the distribution of the pain and identification of a lesion in neural structures that innervate this region.

Although neuropathic pains can be described in terms of the pain characteristics (continuous or lancinating) or site of injury (for example, neuronopathy or plexopathy), it is useful to distinguish these syndromes according to the presumed site of the aberrant neural activity ("generator") that sustains the pain (42). Peripheral neuropathic pain is caused by injury to a peripheral nerve or nerve root and is presumably sustained by aberrant processes originating in the nerve root, plexus, or nerve. Neuropathic pains believed to be sustained by a central "generator" include sympathetically maintained pain [also known as *reflex sympathetic dystrophy* (RSD) or *causalgia*] and a group of syndromes traditionally known as the *deafferentation pains* (e.g., phantom pain). Sympathetically maintained pain may occur following injury to soft tissue, peripheral nerve, viscera, or central nervous system, and is characterized by focal autonomic dysregulation in a painful region (e.g., vasomotor or pilomotor changes, swelling, or sweating abnormalities) or trophic changes (43). Understanding of "RSD" and "causalgia" and sympathetically maintained pain have undergone considerable review. The International Association for the Study of Pain has suggested classification of these syndromes as Complex Regional Pain Syndromes types I and II, indicating that sympathetically maintained pain is a frequent but variable component of these syndromes. Type I corresponds to RSD and occurs without a definable nerve lesion. Type II, formerly called *causalgia*, refers to cases where a definable nerve lesion is present (44,45).

The pain of peripheral neuropathies may be generated by several pathophysiological mechanisms in both the peripheral and central nervous system: (a) pathologically active or sensitized nociceptors can induce spinal cord hyperexcitability that causes input from mechanoreceptive A-b-fibers (light touching) to be perceived as pain; (b) nociceptor function may be selectively impaired within the allodynic skin such that pain and temperature sensation are impaired but light moving mechanical stimuli can often produce severe pain (dynamic mechanical allodynia); (c) inflammatory reactions of the nerve trunk, mediated by the cytokine tumor necrosis factor-a, can induce ectopic activity in primary afferent nociceptors and thus generate spontaneous pain and allodynia; (d) injury can alter sympathetic nervous system interaction with afferent neurons such that sympathetic fibers can induce further activity in sensitized nociceptors (46).

The diagnosis of neuropathic pain has important clinical implications. The response of neuropathic pains to opioid analgesics is less predictable and generally less dramatic than the response of nociceptive pains. Optimal treatment may depend on the use of so-called adjuvant analgesics (47,48 and 49) or other specific approaches such as somatic or sympathetic nerve block (35).

Idiopathic Pain

Pain that is perceived to be excessive for the extent of identifiable organic pathology can be termed *idiopathic* unless the patient presents with affective and behavioral disturbances that are severe enough to infer a predominating psychological pathogenesis, in which case a specific psychiatric diagnosis (e.g., somatoform disorder) can be applied (50,51). When the inference of a somatoform disorder cannot be made, however, the label *idiopathic* should be retained and assessments should be repeated at appropriate intervals. Idiopathic pain in general, and pain related to a psychiatric disorder specifically, are uncommon in the cancer population, notwithstanding the importance of psychological factors in quality of life.

Stepwise Approach to the Evaluation of Cancer Pain

A practical approach to cancer pain assessment incorporates a stepwise approach that begins with data collection and ends with a clinically relevant formulation.

Data Collection

History

A careful review of past medical history and the chronology of the cancer are important to place the pain complaint in context. The pain-related history must elucidate the relevant pain characteristics, as well as the responses of the patient to previous disease-modifying and analgesic therapies. The presence of multiple pain problems is common. If more than one is reported, each must be assessed independently. The use of validated pain assessment instruments can provide a format for communication between the patient and health care professionals and can also be used to monitor the adequacy of therapy (see the section Pain Measures in Routine Clinical Management).

The clinician should assess the consequences of the pain, including impairment in activities of daily living; psychological, familial, and professional dysfunction; disturbed sleep, appetite, and vitality; and financial concerns. The patient's psychological status, including current level of anxiety or depression, suicidal ideation, and the perceived meaning of the pain, is similarly relevant. Pervasive dysfunctional attitudes, such as pessimism, idiosyncratic interpretation of pain, self-blame, catastrophizing, and perceived loss of personal control, can usually be detected through careful questioning. It is important to assess the patient-family interaction and to note both the kind and frequency of pain behaviors and the nature of the family response.

Most patients with cancer pain have multiple other symptoms (52,53,54,55 and 56). The clinician must evaluate the severity and distress caused by each of these symptoms. Symptom checklists and quality of life measures may contribute to this comprehensive evaluation (57,58).

Examination

A physical examination, including a neurological evaluation, is a necessary part of the initial pain assessment. The need for a thorough neurological assessment is justified by the high prevalence of painful neurological conditions in this population (59,60). The physical examination should attempt to identify the underlying etiology of the pain problem, clarify the extent of the underlying disease, and discern the relationship of the pain complaint to the disease.

Review of Previous Investigations

Careful review of previous laboratory and imaging studies can provide important information about the cause of the pain and the extent of the underlying disease.

Provisional Assessment

The information derived from these data provides the basis for a provisional pain diagnosis, an understanding of the disease status, and the identification of other concurrent concerns. This provisional diagnosis includes inferences about the pathophysiology of the pain and an assessment of the pain syndrome.

Additional investigations are often required to clarify areas of uncertainty in the provisional assessment (59). The extent of diagnostic investigation must be appropriate to the patient's general status and the overall goals of care. For some patients, comprehensive evaluation may require numerous investigations, some targeted at the specific pain problem and others needed to clarify extent of disease or concurrent symptoms. In specific situations, algorithms have been developed to facilitate an efficient evaluation. This is well illustrated by established clinical algorithms for the investigation of back pain in the cancer patient (61,62), which provide a straightforward approach for those patients at highest risk for epidural cord (see the section Algorithm for the Investigation of Cancer Patients with Back Pain).

The lack of a definitive finding on an investigation should not be used to override a compelling clinical diagnosis. In the assessment of bone pain, for example, plain radiographs provide only crude assessment of bony lesions and further investigation with bone scintigrams, computed tomography (CT), or magnetic resonance imaging (MRI) may be indicated. To minimize the risk of error, the physician ordering the diagnostic procedures should personally review them with the radiologist to correlate pathological changes with the clinical findings.

Pain should be managed during the diagnostic evaluation. Comfort will improve compliance and reduce the distress associated with procedures. No patient should be inadequately evaluated because of poorly controlled pain.

The comprehensive assessment may also require evaluation of other physical or psychosocial problems identified during the initial assessment. Expert assistance from other physicians, nurses, social workers, or others may be essential.

Formulation and Therapeutic Planning

The evaluation should enable the clinician to appreciate the nature of the pain, its impact, and concurrent concerns that further undermine quality of life. The findings of this evaluation should be reviewed with the patient. Through candid discussion, current problems can be prioritized to reflect their importance to the patient. This evaluation may also identify potential outcomes that would benefit from contingency planning. Examples include evaluation of resources for home care, prebereavement interventions with the family, and the provision of assistive devices in anticipation of compromised ambulation.

Measurement of Pain and Its Impact on Patient Well-Being

Although pain measurement has generally been used by clinical investigators to determine the impact of analgesic therapies, it has become clear that it has an important role in the routine monitoring of cancer patients in treatment settings (63,64 and 65). Because observer ratings of symptom severity correlate poorly with patient ratings and are generally an inadequate substitute for patient reporting (25), patient self-report is the primary source of information for the measurement of pain.

Pain Measures in Routine Clinical Management

Recent guidelines from the Agency for Health Care Policy and Research (66), American Pain Society (64), and the Joint Commission on Accreditation of Healthcare Organizations (67) recommend the regular use of pain rating scales to assess pain severity and relief in all patients who commence or change treatments. These recommendations also suggest that clinicians teach patients and families to use assessment tools in the home to promote continuity of pain management in all settings. The two most commonly used scales for adults are a verbal descriptor scale (i.e., “Which word best describes your pain: none, mild, moderate, severe, or excruciating?”), or a numerical scale (i.e., “On a scale from 0 to 10, where 0 indicates no pain and 10 indicates the worst pain you can imagine, how would you rate your pain?”) (66,67).

A recent study demonstrated that the use of a simple verbal pain assessment tool improved the caregiver's understanding of pain status in hospitalized patients (65). Regular pain measurement, using a pain scale attached to the bedside chart (Fig. 1-1), has been incorporated into a continuous quality improvement strategy at a cancer center (68) and preliminary data suggest that nursing knowledge and attitudes regarding the assessment and management of cancer pain have improved as a result. In addition to focusing staff attention on symptom assessment, such measures may be used as a means of reviewing the quality of patient care and ascertaining situation-specific barriers to symptom control (69,70).

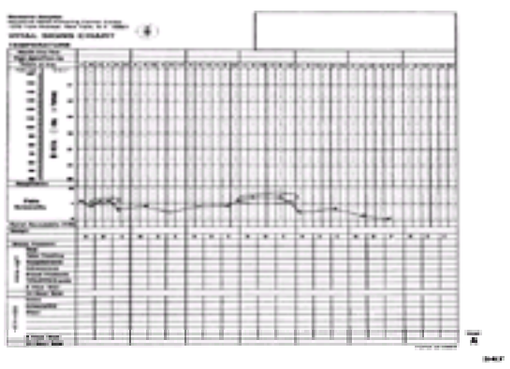

FIGURE 1-1. The patient observation chart from the Memorial Sloan-Kettering Cancer Institute. Incorporated into the chart is a 10-point pain scale and an item regarding the adequacy of pain control.

Instruments for the Measurement of Pain in Research Settings

Pain can be measured using a unidimensional or multidimensional scales. Unidimensional scales generally address intensity or relief using visual analogue, numerical, and categorical scales. Multidimensional instruments include the Memorial Pain Assessment Card (MPAC), the McGill Pain Questionnaire (MPQ), and the Brief Pain Inventory (BPI).

Memorial Pain Assessment Card (MPAC)

The MPAC (71) is a brief, validated measure that uses 100-mm visual analogue scales to characterize pain intensity, pain relief, and mood, and an eight-point verbal rating scale to further characterize pain intensity (Fig. 1-2). The mood scale, which is correlated with measures of global psychological distress, depression, and anxiety, is considered to be a brief measure of global symptom distress (71). Although this instrument does not provide detailed descriptors of pain, its brevity and simplicity may facilitate the collection of useful information while minimizing patient burden and encouraging compliance.

FIGURE 1-2. The Memorial Pain Assessment Card. (Reproduced with permission.)

Brief Pain Inventory (BPI)

The BPI (Fig. 1-3) (72) is a simple and easily administered tool that provides information about pain history, intensity, location, and quality. Numeric scales (range, 1–10) indicate the intensity of pain in general, at its worst, at its least, and right now. A percentage scale quantifies relief from current therapies. A figure representing the body is provided for the patient to shade the area corresponding to his or her pain. Seven questions determine the degree to which pain interferes with function, mood, and enjoyment of life. The BPI is self-administered and easily understood, and has been translated into several languages (73,74 and 75). It is suitable for ongoing evaluation of pain over time.

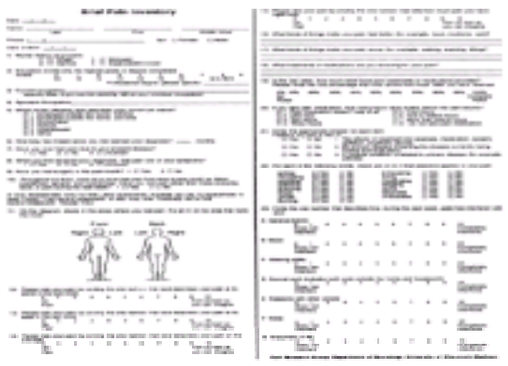

FIGURE 1-3. The Brief Pain Inventory. (Reproduced with permission of the Pain Research Group, Department of Neurology, University of Wisconsin-Madison.)

McGill Pain Questionnaire (MPQ)

The MPQ (76,77) is a self-administered questionnaire that provides global scores and subscale scores that reflect the sensory, affective, and evaluative dimensions of pain. The scores are derived from ratings of pain descriptors selected by the patient. A 5-point verbal categorical scale characterizes the intensity of pain. A pain drawing localizes the pain. Further information is collected about the impact of medications and other therapies. The impact of pain on function is not assessed. Although the MPQ has been extensively evaluated in chronic-pain patients, the utility of the subscale scores has not been demonstrated for cancer pain (78). A short form of the MPQ was developed for use in research settings and has been validated in a palliative care setting (79).

ACUTE PAIN SYNDROMES

Cancer-related acute pain syndromes are most commonly due to diagnostic or therapeutic interventions (80) (Table 1-1). They generally pose little diagnostic difficulty. Although some tumor-related pains have an acute onset (such as pain from a pathological fracture), most of these will persist unless effective treatment for the underlying lesion is provided. A comprehensive pain assessment in such patients is usually valuable, potentially yielding important information about the extent of disease or concurrent issues relevant to therapy.

Acute Pain Associated with Diagnostic and Therapeutic Interventions

Many investigations and treatments are associated with predictable, transient pain. For those patients with a preexisting pain syndrome, otherwise innocuous manipulations can also precipitate an incident pain.

Acute Pain Associated with Diagnostic Interventions

Lumbar Puncture Headache

Lumbar puncture (LP) headache is the best characterized acute pain syndrome associated with a diagnostic intervention. This syndrome is characterized by the delayed development of a positional headache, which is precipitated or markedly exacerbated by upright posture. The pain is believed to be related to reduction in cerebrospinal fluid (CSF) volume, due to ongoing leakage through the defect in the dural sheath, and compensatory expansion of the pain-sensitive intracerebral veins (81,82). The incidence of headache is related to the caliber of the LP needle (0–2% with 27–29-gauge, 0.5–7% with 25–26-gauge, 5–8% with 22-gauge, 10–15% with 20-gauge, and 20–30% with 18-gauge needles) (83,84 and 85). Using a regular bevelled needle, the overall incidence can be reduced by the use of a small-gauge needle and by longitudinal insertion of the needle bevel, which presumably induces less trauma to the longitudinal elastic fibers in the dura (86). Recent evidence suggests that the use of a nontraumatic, conical-tipped needle with a lateral opening spreads the dural fibers and is associated with a substantially lesser risk of post-LP headaches than regular cannulae (84,87,88 and 89). The evidence that recumbency after LP reduces the incidence of this syndrome is controversial (90).

LP headache, which usually develops hours to several days after the procedure, is typically described as a dull occipital discomfort that may radiate to the frontal region or to the shoulders (81,83,91,92 and 93). Pain is commonly associated with nausea and dizziness (91). When severe, the pain may be associated with diaphoresis and vomiting (91,94). The duration of the headache is usually 1–7 days (94,95), and routine management relies on rest, hydration, and analgesics (92). Persistent headache may necessitate application of an epidural blood patch (92). Although a recent controlled study suggested that prophylactic administration of a blood patch may reduce this complication (96), the incidence and severity of the syndrome do not warrant this treatment. Severe headache has also been reported to respond to treatment with intravenous or oral caffeine (81).

Transthoracic Needle Biopsy

Transthoracic fine-needle aspiration of intrathoracic mass is generally a nonnoxious procedure. Severe pain has, however, been associated with this procedure when the underlying diagnosis was a neurogenic tumor (97).

Transrectal Prostatic Biopsy

Transrectal, ultrasound-guided prostate biopsy is an essential procedure in the diagnosis and management of prostate cancer. In a prospective study, 16% of the patients reported pain of moderate or greater severity (PAS PI ³5) and 19% would not agree to undergo the procedure again without anesthesia (98). Transrectal, ultrasound-guided prostatic nerve blockade is effective in relieving discomfort associated with this procedure (99).

Mammography Pain

Breast compression associated with mammography can cause moderate and, rarely, severe pain (100,101). Unless patients are adequately counseled and treated, occasional patients will refuse repeat mammograms because of pain (100).

Acute Pain Associated with Therapeutic Interventions

Postoperative Pain

Acute postoperative pain is universal unless adequately treated. Undertreatment is endemic despite the availability of adequate analgesic and anesthetic techniques (102,103 and 104). Guidelines for management have been reviewed (103,105). Postoperative pain that exceeds the normal duration or severity should prompt a careful evaluation for the possibility of infection or other complications.

Cryosurgery-Associated Pain and Cramping

Cryosurgery of the cervix in the treatment of intraepithelial neoplasm commonly produces an acute cramping pain syndrome. The severity of the pain is related to the duration of the freeze period and it is not diminished by the administration of prophylactic nonsteroidal anti-inflammatory drugs (106).

Other Interventions

Invasive interventions other than surgery are commonly used in cancer therapy and may also result in predictable acute pain syndromes. Examples include the pains associated with tumor embolization techniques (107) and chemical pleurodesis (108).

Acute Pain Associated with Analgesic Techniques

Local Anesthetic Infiltration Pain

Intradermal and subcutaneous infiltration of lidocaine produces a transient burning sensation before the onset of analgesia. This can be modified with the use of buffered solutions (109). Other maneuvers, including warming of the solution (110) or slowing rate of injection (111), do not diminish injection pain.

Opioid Injection Pain

Intramuscular and subcutaneous injections are painful. When repetitive dosing is required, the intramuscular route of administration is not recommended (66,103). The pain associated with subcutaneous injection is influenced by the volume injected and the chemical characteristics of the injectant. Subcutaneous injection of opioids can produce a painful subdermal reaction. This is infrequently observed with morphine or hydromorphone (112) but common with methadone (113). For this reason, the subcutaneous infusion of methadone is not recommended. There is some data to suggest that the addition of a low concentration of dexamethasone may reduce the likelihood of local irritation (114).

Opioid Headache

Rarely patients develop a reproducible generalized headache after opioid administration. Although its cause is not known, speculation suggests that it may be caused by opioid-induced histamine release.

Spinal Opioid Hyperalgesia Syndrome

Intrathecal and epidural injection of high opioid doses is occasionally complicated by pain (typically perineal, buttock, or leg), hyperalgesia, and associated manifestations, including segmental myoclonus, piloerection, and priapism. This is an uncommon phenomenon that remits after discontinuation of the infusion (115,116 and 117).

Epidural Injection Pain

Back, pelvic, or leg pain may be precipitated by epidural injection or infusion. The incidence of this problem has been estimated at approximately 20% (118). It is speculated that it may be caused by the compression of an adjacent nerve root by the injected fluid (118).

Acute Pain Associated with Anticancer Therapies

Acute Pain Associated with Chemotherapy Infusion Techniques

Intravenous Infusion Pain

Pain at the site of cytotoxic infusion is a common problem. Four pain syndromes related to intravenous infusion of chemotherapeutic agents are recognized: venous spasm, chemical phlebitis, vesicant extravasation, and anthracycline-associated flare. Venous spasm causes pain that is not associated with inflammation or phlebitis, and which may be modified by application of a warm compress or reduction of the rate of infusion. Chemical phlebitis can be caused by cytotoxic medications including amasarcine, dacarbazine, carmustine (119,120), and vinorelbine (121), as well as the infusion of potassium chloride and hyperosmolar solutions (122). The pain and linear erythema associated with chemical phlebitis must be distinguished from the more serious complication of a vesicant cytotoxic extravasation (Table 1-4) (123,124). Vesicant extravasation may produce intense pain followed by desquamation and ulceration (123,124). Finally, a brief venous flare reaction is often associated with intravenous administration of the anthracycline, doxorubicin. The flare is typically associated with local urticaria and occasionally patients report pain or stinging (125,126).

Amasarcine	Mitomycin-C
BCNU	Mitoxantrone
Cis-platinum	Streptozotocin
Dacarbazine	Teniposide
Daunorubicin	Vinblastine
Doxorubicin	Vincristine
Etoposide	Vindesine

BCNU, bischloroethyl-nitrosurea (carmustine).

TABLE 1-4. COMMONLY USED TISSUE VESICANT CYTOTOXIC DRUGS

Hepatic Artery Infusion Pain

Cytotoxic infusions into the hepatic artery (for patients with hepatic metastases) are often associated with the development of a diffuse abdominal pain (127). Continuous infusions can lead to persistent pain. In some patients, the pain is due to the development of gastric ulceration or erosions (128), or cholangitis (129). If the latter complications do not occur, the pain usually resolves with discontinuation of the infusion. A dose relationship is suggested by the observation that some patients will comfortably tolerate reinitiating of the infusion at a lower dose (130).

Intraperitoneal Chemotherapy Pain

Abdominal pain is a common complication of intraperitoneal chemotherapy. A transient mild abdominal pain, associated with sensations of fullness or bloating, is reported by approximately 25% of patients (131). A further 25% of patients reports moderate or severe pain, necessitating opioid analgesia or discontinuation of therapy (131). Moderate or severe pain is usually caused by chemical serositis or infection (132). Drug selection may be a factor in the incidence of chemical serositis. It is a common complication of intraperitoneal use of the anthracycline agents mitoxantrone and doxorubicin and with paclitaxel (Taxol), but it is relatively infrequent with 5-fluorouracil (5-FU) or cisplatinum. Abdominal pain associated with fever and leukocytosis in blood and peritoneal fluid is suggestive of infectious peritonitis (133).

Intravesical Chemotherapy or Immunotherapy

Intravesical bacillus Calmette-Guérin therapy for transitional cell carcinoma of the urinary bladder usually causes a transient bladder irritability syndrome characterized by frequency and/or micturition pain (134). Rarely treatment may trigger a painful polyarthritis (135). Similarly intravesical doxorubicin often causes a painful chemical cystitis (136).

Acute Pain Associated with Chemotherapy Toxicity

Mucositis

Severe mucositis is an almost invariable consequence of the myeloablative chemotherapy and radiotherapy that precedes bone marrow transplantation, but it is less common with standard intensity therapy (137,138 and 139). Although the clinical syndrome usually involves the oral cavity and pharynx, the underlying pathology commonly extends to other gastrointestinal mucosal surfaces. Symptoms may occur as a result of involvement of the esophagus, stomach, or intestine (e.g., odynophagia, dyspepsia, or diarrhea). Damaged mucosal surfaces may become superinfected with microorganisms such as *Candida albicans* and herpes simplex. The latter complication is most likely in neutropenic patients, who are also predisposed to systemic sepsis arising from local invasion by aerobic and anaerobic oral

flora.

Corticosteroid-Induced Perineal Discomfort

A transient burning sensation in the perineum is described by some patients following rapid infusion of large doses (20–100 mg) of dexamethasone (140). Patients need to be warned that such symptoms may occur. Clinical experience suggests that this syndrome is prevented by slow infusion.

Steroid Pseudorheumatism

The withdrawal of corticosteroids may produce a pain syndrome that manifests as diffuse myalgias, arthralgias, and tenderness of muscles and joints. These symptoms occur with rapid or slow withdrawal and may occur in patients taking these drugs for long or short periods of time. The pathogenesis of this syndrome is poorly understood, but it has been speculated that steroid withdrawal may sensitize joint and muscle mechanoreceptors (141). Treatment consists of reinstituting the steroids at a higher dose and withdrawing them more slowly (141).

Painful Peripheral Neuropathy

Chemotherapy-induced painful peripheral neuropathy, which is usually associated with vinca alkaloids, cisplatinum and paclitaxel, can have an acute course. The vinca alkaloids (particularly vincristine) are also associated with other, presumably neuropathic, acute pain syndromes, including pain in the jaw, legs, arms, or abdomen, that may last from hours to days (142,143 and 144). Vincristine-induced orofacial pain in the distribution of the trigeminal and glossopharyngeal nerves occurs in approximately 50% of patients at the onset of vincristine treatment (144). The pain, which is severe in approximately half of those affected, generally begins 2–3 days after vincristine administration and lasts for 1–3 days. It is usually self-limiting and if recurrence occurs, it is usually mild (144). The neuropathy associated with paclitaxel neuropathy is dose related and is generally subacute in onset with a tendency to resolution after the completion of therapy (145).

Headache

Intrathecal methotrexate in the treatment of leukemia or leptomeningeal metastases produces an acute meningitic syndrome in 5–50% of patients (146). Headache is the prominent symptom and may be associated with vomiting, nuchal rigidity, fever, irritability, and lethargy. Symptoms usually begin hours after intrathecal treatment and persist for several days. CSF examination reveals a pleocytosis that may mimic bacterial meningitis. Patients at increased risk for the development of this syndrome include those who have received multiple intrathecal injections and those patients undergoing treatment for proven leptomeningeal metastases (146). The syndrome tends not to recur with subsequent injections.

Systemic administration of L-asparaginase for the treatment of acute lymphoblastic leukemia produces thrombosis of cerebral veins or dural sinuses in 1–2% of patients (147). This complication typically occurs after a few weeks of therapy, but its onset may be delayed until after the completion of treatment. It occurs as a result of depletion of asparagine, which, in turn, leads to the reduction of plasma proteins involved in coagulation and fibrinolysis. Headache is the most common initial symptom, and seizures, hemiparesis, delirium, vomiting, or cranial nerve palsies may also occur. The diagnosis may be established by angiography or by gradient echo sequences on MRI scan (148).

Trans-retinoic acid therapy, which may be used in the treatment of acute promyelocytic leukemia, can cause a transient severe headache (149). The mechanism may be related to pseudotumor cerebri induced by hypervitaminosis A.

Diffuse Bone Pain

Trans-retinoic acid therapy in patients with acute promyelocytic leukemia often produces a syndrome of diffuse bone pain (150,151). The pain is generalized, of variable intensity, and closely associated with a transient neutrophilia. The latter observation suggests that the pain may be due to marrow expansion, a phenomenon that may underlie a similar pain syndrome that occurs following the administration of colony-stimulating factors (152).

Taxol-Induced Arthralgia and Myalgia

Administration of paclitaxel generates a syndrome of diffuse arthralgias and myalgia in 10–20% of patients (153,154). Diffuse joint and muscle pains generally appear 1–4 days after drug administration and persist for 3–7 days. The pathophysiology of this phenomenon has not been well evaluated.

5-Fluorouracil–Induced Anginal Chest Pain

Patients receiving continuous infusions of 5-FU may develop ischemic chest pain (155). Continuous ambulatory electrocardiographic monitoring of patients undergoing 5-FU infusion demonstrated a near three-fold increase in ischemic episodes over pretreatment recordings (156). These electrocardiographic changes were more common among patients with known coronary artery disease. It is widely speculated that coronary vasospasm may be the underlying mechanism (155,156 and 157).

Palmar-Plantar Erythrodysesthesia Syndrome

Protracted infusion of 5-FU can be complicated by the development of a tingling or burning sensation in the palms and soles followed by the development of an erythematous rash. The rash is characterized by a painful, sharply demarcated, intense erythema of the palms and/or soles followed by bulla formation, desquamation, and healing. Continuous low-dose 5-FU infusion (200–300 mg/m^2/day) will produce this palmar-plantar erythrodysesthesia syndrome in 40–90% of patients (158,159). It occurs rarely with patients undergoing 96- to 120-hour infusions (160). The pathogenesis is unknown. The eruption is self-limiting in nature and it does not usually require discontinuation of therapy. Symptomatic measures are often required (160) and treatment with pyridoxine has been reported to induce resolution of the lesions (161). Palmar-plantar erythrodysesthesia is also commonly observed among patients treated with the orally administered 5-FU prodrug, capecitabine, when it may warrant discontinuation of therapy if severe (162).

A similar syndrome has recently been reported with liposomal doxorubicin, which is thought to be relatively sequestered in skin (163). As with 5-FU, this is also a dose-related adverse effect related to repeated dosing. Uncommonly palmar-plantar erythrodysesthesia has been observed with paclitaxel (164).

Postchemotherapy Gynecomastia

Painful gynecomastia can occur as a delayed complication of chemotherapy. Testis cancer is the most common underlying disorder (165) but it has been reported after therapy for other cancers as well (166,167). Gynecomastia typically develops after a latency of 2–9 months and resolves spontaneously within a few months. Persistent gynecomastia is occasionally observed (167). Cytotoxic-induced disturbance of androgen secretion is the probable cause of this syndrome (165). In the patient with testicular cancer, this syndrome must be differentiated from tumor-related gynecomastia, which may be associated with early recurrence (see the section Tumor-Related Gynecomastia) (168,169).

Chemotherapy-Induced Acute Digital Ischemia

Raynaud's phenomenon or transient ischemia of the toes is a common complication of bleomycin, vinblastine, and cisplatin treatment for testicular cancer (170). Rarely, irreversible digital ischemia leading to gangrene has been reported after bleomycin (171).

Chemotherapy-Induced Tumor Pain

Pain at the site of tumor is reported to occur in some patients (7%) after treatment with vinorelbine. Typically, pain begins within a few minutes of the vinorelbine infusion, is moderate to severe in intensity, and requires analgesic therapy. Premedication with ketorolac may prevent recurrence in some cases (172,173 and 174).

Acute Pain Associated with Hormonal Therapy

Luteinizing Hormone-Releasing Factor Tumor Flare in Prostate Cancer

Initiation of luteinizing hormone-releasing factor (LRF) hormonal therapy for prostate cancer produces a transient symptom flare in 5–25% of cases (175,176). The flare is presumably caused by an initial stimulation of luteinizing hormone release before suppression is achieved. The syndrome typically presents as an exacerbation of

bone pain or urinary retention; spinal cord compression and sudden death have been reported (177). Symptom flare is usually observed within the first week of therapy, and lasts 1–3 weeks in the absence of androgen antagonist therapy. Coadministration of an androgen antagonist during the initiation of LRF agonist therapy can prevent this phenomenon (178). Among patients with prostate cancer that is refractory to first-line hormonal therapy, transient tumor flares have been observed with androstenedione (179,180) and medroxyprogesterone (181).

Hormone-Induced Pain Flare in Breast Cancer

Any hormonal therapy for metastatic breast cancer can be complicated by a sudden onset of diffuse musculoskeletal pain commencing within hours to weeks of the initiation of therapy (182). Other manifestations of this syndrome include erythema around cutaneous metastases, changes in liver function studies, and hypercalcemia. Although the underlying mechanism is not understood, this does not appear to be caused by tumor stimulation, and it is speculated that it may reflect normal tissue response (183).

Acute Pain Associated with Immunotherapy

Virtually all patients treated with interferon (IFN) experience an acute syndrome consisting of fever, chills, myalgias, arthralgias, and headache (184). The syndrome usually begins shortly after initial dosing and frequently improves with continued administration of the drug (184). The severity of symptoms is related to type of IFN, route of administration, schedule, and dose. Doses of 1–9 million units of IFN-a are usually well tolerated, but doses greater than or equal to 18 million units usually produce moderate to severe toxicity (184). Acetaminophen pretreatment is often useful in ameliorating these symptoms.

Acute Pain Associated with Bisphosphonates

Bisphosphonates are widely used in the care of patients with bony metastases, especially among patients with breast cancer and myeloma (185). Infusion of bisphosphonates is sometimes associated with the development of multifocal bone pain and/or myalgia. Typically, pain occurs within 24 hours of infusion and may last up to 3 days. Pain intensity is variable and may be severe. The condition is self-limiting but may require analgesic therapy (186).

Acute Pain Associated with Growth Factors

Colony-stimulating factors are hematopoietic growth hormones that stimulate the production, maturation, and function of white blood cells. Granulocyte-macrophage colony-stimulating factors and granulocyte colony-stimulating factors and interleukin-3 commonly produce mild to moderate bone pain and constitutional symptoms such as fever, headache, and myalgias during the period of administration (187,188).

Subcutaneous administration of recombinant human erythropoietin a (r-HuEPO-a) is associated with pain at the injection site in approximately 40% of cases (189). Subcutaneous injection of r-HuEPO-a is more painful than r-HuEPO-b (190). Alpha erythropoietin injection pain can be reduced by dilution of the vehicle with benzyl alcohol saline, reduction of the volume of the vehicle to 1.0–0.1 ml (191), or addition of lidocaine (192).

Acute Pain Associated with Radiotherapy

Incident pains can be precipitated by transport and positioning of the patient for radiotherapy. Other pains can be caused by acute radiation toxicity, which is most commonly associated with inflammation and ulceration of skin or mucous membranes within the radiation port. The syndrome produced is dependent upon the involved field: Head and neck irradiation can cause a stomatitis or pharyngitis (139), treatment of the chest and esophagus can cause an esophagitis (193), and pelvic therapy can cause a proctitis, cystitis-urethritis, vaginal ulceration, or radiation dermatitis.

Oropharyngeal Mucositis

Radiotherapy-induced mucositis is invariable with doses above 1000 cGy, and ulceration is common at doses above 4000 cGy. Although the severity of the associated pain is variable, it is often severe enough to interfere with oral alimentation. Painful mucositis can persist for several weeks after the completion of the treatment (139,194).

Acute Radiation Enteritis and Proctocolitis

Acute radiation enteritis occurs in as many as 50% of patients receiving abdominal or pelvic radiotherapy. Involvement of the small intestine can present with cramping abdominal pain associated with nausea and diarrhea (195). Pelvic radiotherapy can cause a painful proctocolitis, with tenesmic pain associated with diarrhea, mucous discharge, and bleeding (196). These complications typically resolve shortly after completion of therapy, but may have a slow resolution over 2–6 months (195,196 and 197). Acute enteritis is associated with an increased risk of late onset radiation enteritis (see the section Chronic Radiation Enteritis and Proctitis).

Early Onset Brachial Plexopathy

A transient brachial plexopathy has been described in breast cancer patients immediately following radiotherapy to the chest wall and adjacent nodal areas. In retrospective studies, the incidence of this phenomenon has been variably estimated as 1.4–20.0% (198,199); clinical experience suggests that lower estimates are more accurate. The median latency to the development of symptoms was 4.5 months (3–14 months) in one survey (198). Paresthesias are the most common presenting symptom, and pain and weakness occur less frequently. The syndrome is self-limiting and does not predispose to the subsequent development of delayed onset, progressive plexopathy.

Subacute Radiation Myelopathy

Subacute radiation myelopathy is an uncommon phenomenon that may occur following radiotherapy of extraspinal tumors (200,201). It is most frequently observed involving the cervical cord after radiation treatment of head and neck cancers and Hodgkin's disease. In the latter case, patients develop painful, shock-like pains in the neck that are precipitated by neck flexion (Lhermitte's sign). These pains may radiate down the spine and into one or more extremities. The syndrome usually begins weeks to months after the completion of radiotherapy, and typically resolves over a period of 3–6 months (200).

Radiopharmaceutical-Induced Pain Flare

Strontium-89, Rhenium-186 hydroxyethylidene diphosphonate, and Samarium-153 are systemically administered beta-emitting calcium analogues that are taken up by bone in areas of osteoblastic activity and which may help relieve pain caused by blastic bony metastases (202). A “flare” response, characterized by transient worsening of pain 1–2 days after administration, occurs in 15–20% of patients (203). This flare usually resolves after 3–5 days and most affected patients subsequently develop a good analgesic response (203).

Acute Pain Associated with Infection

A significantly increased incidence of acute herpetic neuralgia occurs among cancer patients, especially those with hematological or lymphoproliferative malignancies and those receiving immunosuppressive therapies (204,205). Pain or itch usually precedes the development of the rash by several days and may occasionally occur without the development of skin eruption (205,206). The pain, which may be continuous or lancinating, usually resolves within 2 months (206). Pain persisting beyond this interval is referred to as *postherpetic neuralgia* (see the section Postherpetic Neuralgia). Patients with active tumor are more likely to have a disseminated infection (204). In those predisposed by chemotherapy, the infection usually develops less than 1 month after the completion of treatment. The dermatomal location of the infection is often associated with the site of the malignancy (204): Patients with primary tumors of gynecological and genitourinary origin have a predilection to lumbar and sacral involvement, and those with breast or lung carcinomas tend to present with thoracic involvement; patients with hematological tumors appear to be predisposed to cervical lesions. The infection also occurs twice as frequently in previously irradiated dermatomes as nonradiated areas.

Acute Pain Associated with Vascular Events

Acute Thrombosis Pain

Thrombosis is the most frequent complication and the second cause of death in patients with overt malignant disease (207). Thrombotic episodes may precede the diagnosis of cancer by months or years and represent a potential marker for occult malignancy (208). Postoperative deep vein thrombosis is more frequent in patients

operated on for malignant diseases than for other disorders, and both chemotherapy and hormone therapy are associated with an increased thrombotic risk (208).

Possible prothrombic factors in cancer include the capacity of tumor cells and their products to interact with platelets, clotting and fibrinolytic systems, endothelial cells, and tumor-associated macrophages. Cytokine release, acute phase reaction, and neovascularization may contribute to in vivo clotting activation (207,208). Patients with pelvic tumors (209), pancreatic cancer (210), gastric cancer, advanced breast cancer (211), and brain tumors (212) are at greatest risk.

Lower-Extremity Deep Venous Thrombosis

Pain and swelling are the most common presenting features of lower-extremity deep vein thrombosis (213). The pain is variable in severity and it is often mild. It is commonly described as a dull cramp, or diffuse heaviness. The pain most commonly affects the calf but may involve the sole of the foot, the heel, the thigh, the groin, or pelvis. Pain usually increases on standing and walking. On examination, suggestive features include swelling, warmth, dilatation of superficial veins, tenderness along venous tracts, and pain induced by stretching (213).

Rarely, patients may develop tissue ischemia or frank gangrene, even without arterial or capillary occlusion. This syndrome is called *phlegmasia cerulea dolens*. It is most commonly seen in patients with underlying neoplasm (214,215) and is characterized by severe pain, extensive edema, and cyanosis of the legs. Gangrene can occur unless the venous obstruction is relieved. When possible, optimal therapy is anticoagulation and thrombectomy (216). The mortality rate for ischemic venous thrombosis is approximately 40%, the cause of death usually being the underlying disease or pulmonary emboli (215).

Upper-Extremity Deep Venous Thrombosis

Only 2% of all cases of deep venous thrombosis involve the upper extremity, and the incidence of pulmonary embolism related to thrombosis in this location is approximately 12% (217). The three major clinical features of upper-extremity venous thrombosis are edema, dilated collateral circulation, and pain (218). Approximately two-thirds of patients have arm pain. Among patients with cancer, the most common causes are central venous catheterization and extrinsic compression by tumor (218). Although thrombosis secondary to intrinsic damage usually responded well to anticoagulation alone and rarely causes persistent symptoms, when extrinsic obstruction is the cause, persistent arm swelling and pain are commonplace (219).

Superior Vena Cava Obstruction

Superior vena cava (SVC) obstruction is most commonly caused by extrinsic compression by enlarged mediastinal lymph nodes (220). In contemporary series lung cancer and lymphomas are the most commonly associated conditions. Increasingly, thrombosis of the SVC is caused by intravascular devices (221), particularly with left-sided ports and when the catheter tip lies in the upper part of the vena (222). Patients usually present with facial swelling and dilated neck and chest wall veins. Chest pain, headache, and mastalgia are less common presentations.

Acute Mesenteric Vein Thrombosis

Acute mesenteric vein thrombosis is most commonly associated with hypercoagulability states. Rarely, it has been associated with extrinsic venous compression by malignant lymphadenopathy (223), extension of venous thrombosis (224), or as a result of iatrogenic hypercoagulable state (225).

CHRONIC PAIN SYNDROMES

Most chronic cancer-related pains are caused directly by the tumor (Table 1-2). Data from the largest prospective survey of cancer pain syndromes revealed that almost one-fourth of the patients experienced two or more pains. Over 90% of the patients had one or more tumor-related pains and 21% had one or more pains caused by cancer therapies. Somatic pains (71%) were more common than neuropathic (39%) or visceral pains (34%) (8). Bone pain and compression of neural structures are the two most common causes (33,226,227,228 and 229).

Bone Pain

Bone metastases are the most common cause of chronic pain in cancer patients (33,226,227,228 and 229). Cancers of the lung, breast, and prostate most often metastasize to bone, but any tumor type may be complicated by painful bony lesions. Although bone pain is usually associated with direct tumor invasion of bony structures, more than 25% of patients with bony metastases are pain-free (230), and patients with multiple bony metastases typically report pain in only a few sites. The factors that convert a painless lesion to a painful one are unknown. Bone metastases could potentially cause pain by any of multiple mechanisms, including endosteal or periosteal nociceptor activation (by mechanical distortion or release of chemical mediators) or tumor growth into adjacent soft tissues and nerves (231). Recent studies have demonstrated that tumor osteolysis may be mediated by a cascade involving the secretion of tumor-produced parathyroid hormone-related protein, which stimulates osteoclastic bone resorption, thus releasing transforming growth factor b, which is abundant in bone matrix. The released transforming growth factor b further promotes osteolysis by stimulating tumor-produced parathyroid hormone-related protein production by tumor cells (232).

Bone pain due to metastatic tumor needs to be differentiated from less common causes. Nonneoplastic causes in this population include osteoporotic fractures (including those associated with multiple myeloma), focal osteonecrosis, which may be idiopathic or related to chemotherapy, corticosteroids (233), or radiotherapy (see the section Osteoradionecrosis) (234).

Multifocal or Generalized Bone Pain

Bone pain may be focal, multifocal, or generalized. Multifocal bone pains are most commonly experienced by patients with multiple bony metastases. A generalized pain syndrome, which is well recognized in patients with multiple bony metastases, is also rarely produced by replacement of bone marrow (235,236). This bone marrow replacement syndrome has been observed in hematogenous malignancies (237,238) and, less commonly, solid tumors (236). This syndrome can occur in the absence of abnormalities on bone scintigraphy or radiography, increasing the difficulty of diagnosis. Rarely, a paraneoplastic osteomalacia can mimic multiple metastases (234).

Vertebral Syndromes

The vertebrae are the most common sites of bony metastases. More than two-thirds of vertebral metastases are located in the thoracic spine; lumbosacral and cervical metastases account for approximately 20% and 10%, respectively (239,240). Multiple level involvement is common, occurring in greater than 85% of patients (241). The early recognition of pain syndromes due to tumor invasion of vertebral bodies is essential, because pain usually precedes compression of adjacent neural structures and prompt treatment of the lesion may prevent the subsequent development of neurological deficits. Several factors often confound accurate diagnosis; referral of pain is common, and the associated symptoms and signs can mimic a variety of other disorders, both malignant (e.g., paraspinal masses) and nonmalignant.

Atlantoaxial Destruction and Odontoid Fracture

Nuchal or occipital pain is the typical presentation of destruction of the atlas or fracture of the odontoid process. Pain often radiates over the posterior aspect of the skull to the vertex and is exacerbated by movement of the neck, particularly flexion (242). Pathological fracture may result in secondary subluxation with compression of the spinal cord at the cervicomedullary junction. This complication is usually insidious and may begin with symptoms or signs in one or more extremity. Typically, there is early involvement of the upper extremities and the occasional appearance of so-called “pseudo-levels” suggestive of more caudal spinal lesions; these deficits can slowly progress to involve sensory and motor function (243). MRI is probably the best method for imaging this region of the spine (244), but clinical experience suggests that CT is also sensitive. Plain radiography, tomography, and bone scintigraphy should be viewed as ancillary procedures.

C7-T1 Syndrome

Invasion of the C7 or T1 vertebra can result in pain referred to the interscapular region. These lesions may be missed if radiographical evaluation is mistakenly targeted to the painful area caudal to the site of damage. Additionally, visualization of the appropriate region on routine radiographs may be inadequate due to obscuration by overlying bone and mediastinal shadows. Patients with interscapular pain should therefore undergo radiography of both the cervical and the thoracic spine. Bone scintigraphy may assist in targeting additional diagnostic imaging procedures such as CT or MRI. The latter procedures can be useful in assessing the possibility that pain is referred from an extraspinal site such as the paraspinal gutter.

T12-L1 Syndrome

A T12 or L1 vertebral lesion can refer pain to the ipsilateral iliac crest or the sacroiliac joint. Imaging procedures directed at pelvic bones can miss the source of the pain.

Sacral Syndrome

Severe focal pain radiating to buttocks, perineum, or posterior thighs may accompany destruction of the sacrum (245,246 and 247). The pain is often exacerbated by sitting or lying and is relieved by standing or walking. The neoplasm can spread laterally to involve muscles that rotate the hip (e.g., the pyriformis muscle). This may produce severe incident pain induced by motion of the hip, or a malignant “pyriformis syndrome” characterized by buttock or posterior leg pain that is exacerbated by internal rotation of the hip. Local extension of the tumor mass may also involve the sacral plexus (see the section Lumbosacral Plexopathy).

Imaging Investigations of Bone Pain

The two most important imaging modalities for the evaluation of bone pain are plain radiography and nuclear bone scan. In general, CT and MRI scans are reserved for situations when the diagnosis cannot be discerned from clinical information and these baseline tests or when there are specific diagnostic issues to be resolved that require special techniques.

Plain Radiography

Radiography should be the first test ordered in the evaluation of bone pain and to confirm findings of other imaging studies. There are three radiographical patterns of metastatic disease: osteolytic, osteoblastic, and mixed. Osteoblastic areas correspond to the reaction of the host bone to the metastases. This reactive bone forms in a random pattern lacking normal bone structure and it often lacks mechanical strength despite its sclerotic, radiopaque appearance. Lytic lesions with little or no reactive bone formation indicate bone destruction in excess of bone formation. Periosteal thickening or elevation is commonly seen with primary bone neoplasms, rapidly growing tumor, or a stress fracture through the underlying bone.

When examining bone radiographs of long bones, it is important to evaluate the extent of cortical destruction. The risk of pathological fracture is high if 50% or more of the cortex is destroyed by tumor (248,249 and 250). Vertebral bodies must be carefully examined for collapse of the vertebral bodies (best viewed on a lateral radiograph) and pedicle erosion (viewed on an anterior/posterior radiograph) because both of these findings are associated with enhanced risk of epidural encroachment by tumor.

Bone Scan

Technetium bisphosphonate bone scans are valuable in evaluating patients with multifocal pain and in identifying the extent of bony secondaries (251). Three patterns of uptake may indicate bony metastases. Most commonly, the radioisotope accumulates in the reactive new bone giving rise to a “hot spot.” Less frequently metastases give rise to cold spots due to the complete absence of reactive bone or poor blood flow (252) or to a pattern of diffuse accumulation of tracer throughout the skeleton (super scan) in the setting of disseminated skeletal disease.

There are several problems associated with bone scans:

1. Bone scans are characterized by high sensitivity and low specificity. Uptake may occur at any skeletal site with an elevated rate of bone turnover such as trauma (even remote trauma), infection, arthropathy, or even acute osteopenia of disuse (251,253,254 and 255). Whereas a scan showing multiple lesions strongly suggests metastases, only 50% of solitary foci represent metastases and, in such cases, radiographical correlation is essential.
2. Because bone scans do not evaluate the structural integrity of the bone, positive findings that correspond to painful sites should be further evaluated by plain radiographs, CT scan, or both.
3. There are some situations in which bone scans are notoriously unreliable. Cancers, such as melanoma and multiple myeloma, may evoke little reactive bone formation, leading to false-negative scans (256,257 and 258). In these situations, plain radiography is the preferred initial examination.

Other radionucleotide bone scanning techniques are occasionally used. Single-photon-emission CT scanning is a bone scanning technique with improved sensitivity and specificity over conventional bone scanning techniques (251,259). In patients with diffuse tracer uptake, bone marrow scanning using tracer linked to antigranulocyte antibody can be helpful in distinguishing a normal scan from a super-scan caused by diffuse marrow infiltration (260). Gallium scanning is useful for detecting otherwise undetected bone metastases from lymphomas and soft-tissue sarcomas (261).

Computed Tomography

CT is a second-tier investigation technique in the evaluation of bony secondaries. It is very effective in evaluating the three-dimensional integrity of bone and to better visualize abnormal lesions identified on bone scan (262). It may be useful in confirming suspicions raised by bone scans and more clearly illustrating the extent of bone destruction. It is particularly helpful in the evaluation of patients with pain in the regions of the pelvic and shoulder girdles and base of skull who have equivocal or nondiagnostic findings on plain radiography. Spine lesions can also be well visualized by CT. With contemporary CT equipment and techniques the additional yield from MRI is usually very limited.

When confirmation of histological diagnosis is required, CT-guided biopsy or fine-needle aspiration is usually diagnostic (263,264 and 265). When the lesion is osteolytic, CT-guided needle biopsy is usually satisfactory (diagnostic accuracy, 80%). When the lesion is osteoblastic or there is a thick overlying cortical rim, it is extremely difficult to insert a needle and obtain an adequate tissue sample. Such cases may necessitate open surgical biopsy.

Magnetic Resonance Imaging

This imaging technique is generally reserved for three clinical situations: (a) to arbitrate suspicious lesions that remain ill-defined despite plain radiography and CT, (b) when bone marrow infiltration is suspected, and (c) in the evaluation of spinal cord compression.

MRI is an excellent method to evaluate bone marrow involvement in disease such as leukemia, lymphoma, and multiple myeloma that replace the marrow space. Because bone marrow (including hematopoietic or “red” marrow) contains a high percentage of fat, T1-weighted MRI scans generally reveal metastases as focal areas of low signal intensity (266). This approach has also been shown to be very sensitive in solid tumors that metastasize to bone marrow such as breast and lung cancer (267,268 and 269).

It is often difficult to distinguish between changes caused by treatment, fracture, and tumor. Indeed, noncontrast MRI cannot reliably distinguish among these changes. In one study the false-positive tumor detection rate was as high as 50% (270). More recent data suggests that gadolinium-enhanced bone imaging can be helpful in this situation; tumor commonly demonstrates high or inhomogeneous signal intensity after gadolinium injection that is not seen in fractures or postoperative changes (271).

Back Pain and Epidural Compression

Epidural compression (EC) of the spinal cord or cauda equina is the second most common neurological complication of cancer, occurring in up to 10% of patients (62). In the community setting, EC is often the first recognized manifestation of malignancy (272); at a cancer hospital it is the presenting syndrome in only 8% of cases (62). Most EC is caused by posterior extension of vertebral body metastasis to the epidural space (Fig. 1-4). Occasionally, EC is caused by tumor extension from the posterior arch of the vertebra or infiltration of a paravertebral tumor through the intervertebral foramen (Fig. 1-5).

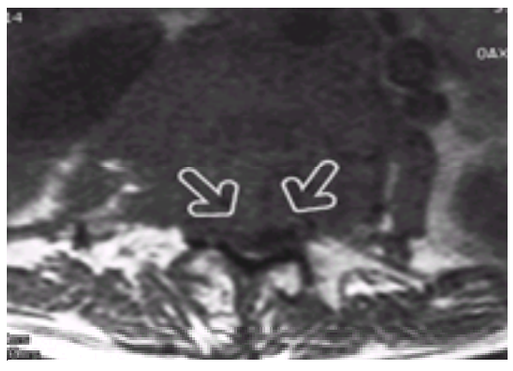

FIGURE 1-4. Axial magnetic resonance imaging scan of the lumbar spine in a 56-year-old woman with carcinoma of the colon who presented with back pain and L3 radicular pain in the right leg. The axial scan performed through L3 demonstrates complete obliteration of the epidural space (*arrows*) and severe compression of the thecal sac.

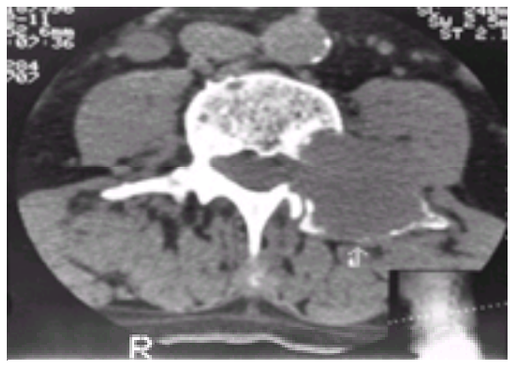

FIGURE 1-5. Computed tomography scan of lumbar vertebra demonstrating a large metastasis involving the left transverse process, invading into the intervertebral foramen and encroaching into the epidural space.

Untreated, EC leads inevitably to neurological damage. Effective treatment can potentially prevent these complications. The most important determinate of the efficacy of treatment is the degree of neurological impairment at the time therapy is initiated. Seventy-five percent of patients who begin treatment while ambulatory remain so. The efficacy of treatment declines to 30–50% for those who begin treatment while markedly paretic and is 10–20% for those who are plegic (239,273,274,275,276,277,278,279,280 and 281). Despite this, delays in diagnosis are commonplace (282).

Back pain is the initial symptom in almost all patients with EC (62). In 10% it is the only symptom at the time of diagnosis (283). Because pain usually precedes neurological signs by a prolonged period, it should be viewed as a potential indicator of EC, which can lead to treatment at a time that a favorable response is most likely. Back pain, however, is a nonspecific symptom that can result from bony or paraspinal metastases without epidural encroachment, from retroperitoneal or leptomeningeal tumor, epidural lipomatosis due to steroid administration (284), or from a large variety of other benign conditions. Because it is infeasible to pursue an extensive evaluation in every cancer patient who develops back pain, the complaint should impel an evaluation that determines the likelihood of EC and thereby selects patients appropriate for definitive imaging of the epidural space. The selection process is based on symptoms and signs and the results of simple imaging techniques.

Clinical Features of Epidural Extension

Some pain characteristics are particularly suggestive of epidural extension (285). Rapid progression of back pain in a crescendo pattern is an ominous occurrence (275). Radicular pain, which can be constant or lancinating, has similar implications (285). It is usually unilateral in the cervical and lumbosacral regions and bilateral in the thorax, where it is often experienced as a tight, belt-like band across the chest or abdomen (285). The likelihood of EC is also greater when back or radicular pain is exacerbated by recumbency, cough, sneeze, or strain (274). Other types of referred pain are also suggestive, including Lhermitte's sign (286) and central pain from spinal cord compression, which usually is perceived some distance below the site of the compression and is typically a poorly localized, nondermatomal dysesthesia (62).

Weakness, sensory loss, autonomic dysfunction, and reflex abnormalities usually occur after a period of progressive pain (285). Weakness may begin segmentally if related to nerve root damage or in a multisegmental or pyramidal distribution if the cauda equina or spinal cord, respectively, is injured. The rate of progression of weakness is variable; in the absence of treatment, following the onset of weakness one-third of patients will develop paralysis within 7 days (287). Patients whose weakness progresses slowly have a better prognosis for neurological recovery with treatment than those who progress rapidly (288,289). Without effective treatment, sensory abnormalities, which may also begin segmentally, may ultimately evolve to a sensory level, with complete loss of all sensory modalities below site of injury. The upper level of sensory findings may correspond to the location of the epidural tumor or be below it by many segments (285). Ataxia without pain is the initial presentation of EC in 1% of patients. This finding is presumably due to early involvement of the spinocerebellar tracts (239). Bladder and bowel dysfunction occur late, except in patients with a conus medullaris lesion who may present with acute urinary retention and constipation without preceding motor or sensory symptoms (285).

Other features that may be evident on examination of patients with EC include scoliosis, asymmetrical wasting of paravertebral musculature, and a gibbus (palpable step in the spinous processes). Spinal tenderness to percussion, which may be severe, often accompanies the pain.

Imaging Modalities

Definitive imaging of the epidural space confirms the existence of EC (and thereby indicates the necessity and urgency of treatment), defines the appropriate radiation portals, and determines the extent of epidural encroachment (which influences prognosis and may alter the therapeutic approach) (61). The options for definitive imaging include MRI, myelography, and CT-myelography, or spiral CT without myelographic contrast.

MRI is noninvasive and offers accurate imaging of the vertebrae, intraspinal, and paravertebral structures. When available it is generally the preferred mode of evaluation. A recent study comparing state-of-the-art MRI techniques with CT-myelography demonstrated equivalent sensitivity and specificity (290). Data suggests that a “scanning” midsagittal MRI is clearly inadequate (291). Whenever possible, total spine imaging should be performed because multiple level involvement is common and other sites may be clinically occult. In a recent study of 65 patients with cord compression, 32 (49%) had multiple level involvement and of these, 28 (66%) were clinically occult (292). MRI is relatively contraindicated in patients with severe claustrophobia and certain metallic implants and is absolutely contraindicated for patients with cardiac pacemakers or aneurysm clips. Several other groups who may not be suitable for MRI include very obese patients and those with severe kyphosis or scoliosis.

Previously, myelography was considered the standard examination for imaging the spinal cord (2,293). In contrast to MRI or CT imaging, it is invasive and evaluation may be limited if there is a complete block to the flow of contrast which precludes demonstrating the extent of the compressing lesion. It has the advantages of facilitating simultaneous evaluation of the CSF for cytology when leptomeningeal metastases are part of the differential diagnosis.

Postmyelographic CT is a useful tool that provides additional information about the vertebral and paravertebral structures. It can usually define the extent of the cord compression (294). It may help distinguish between cord compression caused by displaced bony fragments from soft-tissue extension and in the identification of paraspinal tumors with extension through the intervertebral foramina (290).

Besides immediate patient discomfort, myelography is often complicated by postprocedure side effects that include back pain, headache, vomiting, seizures, and adverse neurobehavioral reactions. The risk of adverse effects is related to the gauge and type of needle used (295), the contrast medium (296), and the anatomy of the EC.

Similar to MRI, CT scanning is noninvasive. It provides excellent visualization of the vertebrae, vertebral structural integrity, paravertebral soft tissues, and the vertebral

foramina. The improved resolution observed with contemporary spiral techniques facilitates very clear imaging of the spinal canal contents. Although no comparative data are yet available, in the author's experience, CT scanning of regions identified by either plain radiography or bone scan usually provides excellent visualization of cortical integrity, the intervertebral foramina, and canal contents. Bone and soft-tissue windows are used in a complimentary manner; bone windows allow evaluation of bony integrity and, in particular, of cortical breach; and soft-tissue windows are used to evaluate the contents of the spinal canal. Using this approach we reserve more expensive and less readily available MRI imaging for equivocal cases when leptomeningeal metastases are suspected or when total spinal imaging is required.

Algorithm for the Investigation of Cancer Patients with Back Pain

Given the prevalence and the potential for dire consequences of EC, and the recognition that back pain is a marker of early (and therefore treatable) EC, algorithms have been developed to guide the evaluation of back pain in the cancer patient. The objective of these algorithms is to select a subgroup of patients who should undergo definitive imaging of the epidural space from the large number of patients who develop back pain (61). Effective treatment of EC before irreversible neurological compromise occurs is the overriding goal of these approaches.

One such algorithm defines both the urgency and course of the evaluation (Fig. 1-6). Patients with emerging symptoms and signs indicative of spinal cord or cauda equina dysfunction are designated Group 1. The evaluation (and, if appropriate, treatment) of these patients should proceed on an emergency basis. In most cases, these patients should receive an intravenous dose of corticosteroid before epidural imaging is performed.

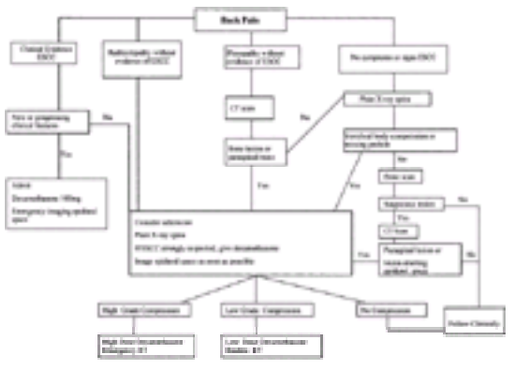

FIGURE 1-6. Algorithm for the management of back pain in the cancer patient. CT, computed tomography; ESCC, extradural spinal cord compression; RT, radiation therapy.

Patients with symptoms and signs of radiculopathy or stable or mild signs of spinal cord or cauda equina dysfunction are designated Group 2. These patients are also usually treated presumptively with a corticosteroid and are scheduled for definitive imaging of the epidural space as soon as possible. Group 3 patients have back pain and no symptoms or signs suggesting EC. These patients should be evaluated in routine fashion starting with plain spine radiographs. The presence at the appropriate level of any abnormality consistent with neoplasm indicates a high probability (60%) of EC (293,297). This likelihood varies, however, with the type of radiological abnormality. For example, one study noted that EC occurred in 87% of patients with greater than 50% vertebral body collapse, 31% with pedicle erosion, and only 7% with tumor limited to the body of the vertebra without collapse (298). Definitive imaging of the epidural space is thus strongly indicated in patients who have >50% vertebral body collapse and is generally recommended for patients with pedicle erosion. Some patients with neoplasm limited to the vertebral body can be followed expectantly. Imaging should be performed if pain progresses or changes (e.g., becomes radicular) or if radiographical evidence of progression is obtained.

Among patients with vertebral collapse, it is often difficult to distinguish malignant from nonmalignant pathology. Vertebral metastases are suggested by destruction of the anterolateral or posterior cortical bone of the vertebral body, the cancellous bone or vertebral pedicle, a focal paraspinal soft-tissue mass, and an epidural mass. Nonmalignant causes are suggested by cortical fractures of the vertebral body without cortical bone destruction, retropulsion of a fragment of the posterior cortex of the vertebral body into the spinal canal, fracture lines within the cancellous bone of the vertebral body, an intravertebral vacuum phenomenon, and a thin diffuse paraspinal soft-tissue mass (299).

Normal spine radiographs alone are not adequate to ensure a low likelihood of epidural tumor in patients with back pain. The bone may not be sufficiently damaged to change the radiograph or the tumor may involve the epidural space with little or no involvement of the adjacent bone (such as may occur when paraspinal tumor grows through the intervertebral foramen). The latter phenomenon has been most strikingly demonstrated in patients with lymphoma, in whom EC presents with normal radiography more than 60% of the time (300,301). Damage to the vertebra that is not seen on the plain radiograph may potentially be demonstrated by bone scintigraphy. In patients with back pain and normal bone radiography, a positive scintigram at the site of pain is associated with a 12–17% likelihood of epidural disease (273,302). Although such patients can also be followed expectantly, definitive imaging of the epidural space should be considered, particularly if the pain is progressive.

If both radiographs and scintigraphy are normal but the patient has severe or progressive pain, evaluation with CT, or preferably MRI, may still be warranted. If the CT scan demonstrates either a bony lesion abutting the spinal canal, a paraspinal mass, or a perivertebral soft-tissue collar, imaging of the epidural space is still justified (273,303).

Pain Syndromes of the Bony Pelvis and Hip

The pelvis and hip are common sites of metastatic involvement. Lesions may involve any of the three anatomical regions of the pelvis (ischiopubic, iliosacral, or periacetabular), the hip joint itself or the proximal femur (304). The weight bearing function of these structures, essential for normal ambulation, contributes to the propensity of disease at these sites to cause incident pain with ambulation.

Hip Joint Syndrome

Tumor involvement of the acetabulum or head of femur typically produces localized hip pain that is aggravated by weight bearing and movement of the hip. The pain may radiate to the knee or medial thigh, and occasionally, pain is limited to these structures (304,305). Medial extension of an acetabular tumor can involve the lumbosacral plexus as it traverses the pelvic sidewall (Fig. 1-7). Evaluation of this region is best accomplished with CT or MRI, both of which can demonstrate the extent of bony destruction and adjacent soft-tissue involvement more sensitively than other imaging techniques (306).

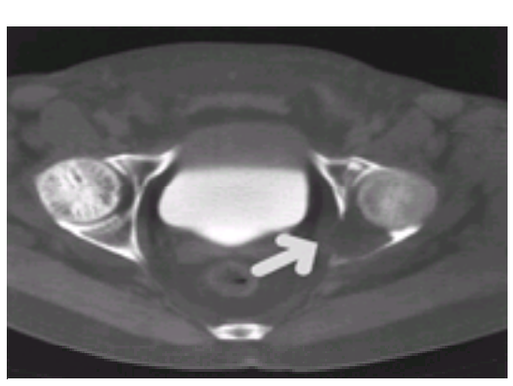

FIGURE 1-7. Computed tomography scan demonstrating lytic lesion of the right acetabulum with tumor extension into the pelvis (*arrow*).

Acrometastases

Acrometastases, metastases in the hands and feet, are rare and often misdiagnosed or overlooked (307). In the feet, the larger bones containing the higher amounts of

red marrow, such as the os calcis, are usually involved (308). Symptoms may be vague and can mimic other conditions such as osteomyelitis, gouty rheumatoid arthritis, Reiter's syndrome, Paget's disease, osteochondral lesions, and ligamentous sprains.

Arthritides

Hypertrophic Pulmonary Osteoarthropathy

Hypertrophic pulmonary osteoarthropathy is a paraneoplastic syndrome that incorporates clubbing of the fingers, periostitis of long bones, and occasionally a rheumatoid-like polyarthritis (309). Periosteitis and arthritis can produce pain, tenderness, and swelling in the knees, wrists, and ankles. The onset of symptoms is usually subacute, and it may precede the discovery of the underlying neoplasm by several months. It is most commonly associated with non–small cell lung cancer. Less commonly it may be associated with benign mesothelioma (310), pulmonary metastases from other sites (311), smooth muscle tumors of the esophagus (312), breast cancer (313), and metastatic nasopharyngeal cancer (314). Effective antitumor therapy is sometimes associated with symptom regression (315). Hypertrophic pulmonary osteoarthropathy is diagnosed on the basis of physical findings, radiological appearance, and radionuclide bone scan (309,316,317).

Other Polyarthritides

Rarely rheumatoid arthritis, systemic lupus erythematosus, and an asymmetrical polyarthritis may occur as paraneoplastic phenomena that resolve with effective treatment of the underlying disease (318,319). A syndrome of palmar plantar fasciitis and polyarthritis, characterized by palmar and digital with polyarticular painful capsular contractions, has been associated with ovarian (320) and breast (321) cancers.

Muscle Pain

Muscle Cramps

Persistent muscle cramps in cancer patients are usually caused by an identifiable neural, muscular, or biochemical abnormality (322). In one series of 50 patients, 22 had peripheral neuropathy, 17 had root or plexus pathology (including six with leptomeningeal metastases), two had polymyositis and one had hypomagnesemia. In this series, muscle cramps were the presenting symptom of recognizable and previously unsuspected neurological dysfunction in 64% (27 of 42) of the identified causes (323).

Skeletal Muscle Tumors

Soft-tissue sarcomas arising from fat, fibrous tissue or skeletal muscle are the most common tumors involving the skeletal muscles. Skeletal muscle is one of the most unusual sites of metastasis from any malignancy (324,325). Lesions are usually painless but they may present with persistent ache.

Headache and Facial Pain

Headache in the cancer patient results from traction, inflammation, or infiltration of pain-sensitive structures in the head or neck. Early evaluation with appropriate imaging techniques may identify the lesion and allow prompt treatment, which may reduce pain and prevent the development of neurological deficits (326).

Intracerebral Tumor

Among 183 patients with new onset chronic headache as an isolated symptom, investigation revealed underlying tumor in 15 cases (327). The prevalence of headache in patients with brain metastases or primary brain tumors is 60–90% (328,329). The headache is presumably produced by traction on pain-sensitive vascular and dural tissues. Patients with multiple metastases and those with posterior fossa metastases are more likely to report this symptom (328). The pain may be focal, overlying the site of the lesion, or generalized. Headache has lateralizing value, especially in patients with supratentorial lesions (329). Posterior fossa lesions often cause a bifrontal headache. The quality of the headache is usually throbbing or steady and the intensity is usually mild to moderate (329).

Among children clinical features predictive of underlying tumor include sleep-related headache, headache in the absence of a family history of migraine, vomiting, absence of visual symptoms, headache of less than 6 months duration, confusion, and abnormal neurological examination findings (330).

The headache is often worse in the morning and is exacerbated by stooping, sudden head movement, or Valsalva maneuvers (cough, sneeze, or strain) (329). In patients with increased intracranial pressure, these maneuvers can also precipitate transient elevations in intracranial pressure called “plateau waves.” These plateau waves, which may also be spontaneous, can be associated with short periods of severe headache, nausea, vomiting, photophobia, lethargy, and transient neurological deficits (331,332). Occasionally these plateau waves produce life-threatening herniation syndromes (331,332).

Leptomeningeal Metastases

Leptomeningeal metastases, which are characterized by diffuse or multifocal involvement of the subarachnoid space by metastatic tumor, occur in 1–8% in patients with systemic cancer (333). Non-Hodgkin's lymphoma and acute lymphocytic leukemia both demonstrate predilection for meningeal metastases (333). The incidence is lower for solid tumors alone. Of solid tumors, adenocarcinomas of the breast and small cell lung cancer predominate (334).

Leptomeningeal metastases present with focal or multifocal neurological symptoms or signs that may involve any level of the neuraxis (333,335,336). More than one-third of patients presents with evidence of cranial nerve damage, including double vision, hearing loss, facial numbness, and decreased vision (335,336). This is particularly true among patients with underlying hematological malignancy (336). Less common features include seizures, papilledema, hemiparesis, ataxic gait, and confusion (337). Generalized headache and radicular pain in the low back and buttocks are the most common pains associated with leptomeningeal metastases (335,336,338). The headache is variable and may be associated with changes in mental status (e.g., lethargy, confusion, or loss of memory), nausea, vomiting, tinnitus, or nuchal rigidity. Pains that resemble cluster headache (339) or glossopharyngeal neuralgia with syncope (340) have also been reported.

The diagnosis of leptomeningeal metastases is confirmed through analysis of the CSF. The CSF may reveal elevated pressure, elevated protein, depressed glucose, and/or lymphocytic pleocytosis. Ninety percent of patients ultimately show positive cytology, but multiple evaluations may be required. After a single LP, the false-negative rate may be as high as 55%; this falls to only 10% after three LPs (335,338,341). The sensitivity and specificity of CSF cytology is enhanced by the use of fluorescence *in situ* hybridization (342,343) or immunocytochemical techniques (344). Tumor markers, such as lactic dehydrogenase isoenzymes (335), carcinoembryonic antigen (345), b_2-microglobulin (345), and tissue polypeptide antigen (346), may help to delineate the diagnosis. Flow cytometry for detection of abnormal DNA content may be a useful adjunct to cytologic examination (347).

Gadolinium-enhanced MRI imaging of the neuroaxis can assist in identifying leptomeningeal metastases (Fig. 1-8). When headache is the presenting feature, gadolinium-enhanced MR examination of the brain is the initial imaging investigation, especially if signs of cranial nerve involvement are present (348,349). If this is nondiagnostic and if the pain distribution indicates spinal involvement, sensitivity is enhanced by performing an examination of the whole spine (Fig. 1-4). There is evidence that gadolinium-enhanced spinal MRI may be positive in almost 50% of patients without clinical findings related to the spinal region and in 60% of patients with negative CSF cytology (350). Additionally, findings of contrast enhancement of the basilar cisterns, parenchymal metastases, hydrocephalus without a mass lesion, or spinal subarachnoid masses or enhancement may all have therapeutic implications (333).

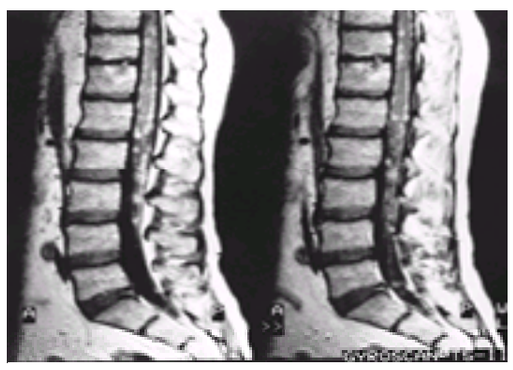

FIGURE 1-8. Gadolinium-enhanced magnetic resonance imaging scan of the thoracolumbar spine demonstrating multifocal meningeal enhancement consistent with leptomeningeal metastases.

Untreated leptomeningeal metastases cause progressive neurological dysfunction at multiple sites, followed by death in 4 to 6 weeks. Current treatment strategies, which includes radiation therapy to the area of symptomatic involvement, corticosteroids, and intraventricular or intrathecal chemotherapy or systemic chemotherapy, are of limited efficacy and in general patient outlook remains poor (337,351,352).

Base of Skull Metastases

Base of skull metastases are associated with well-described clinical syndromes (353), which are named according to the site of metastatic involvement: orbital, parasellar, middle fossa, jugular foramen, occipital condyle, clivus, and sphenoid sinus. Cancers of the breast, lung, and prostate are most commonly associated with this complication (353,354), but any tumor type that metastasizes to bone may be responsible. When base of skull metastases are suspected, axial imaging with CT (including bone window settings) is the usual initial procedure (Fig. 1-9) (353). MRI is more sensitive for assessing soft-tissue extension and CSF analysis may be needed to exclude leptomeningeal metastases.

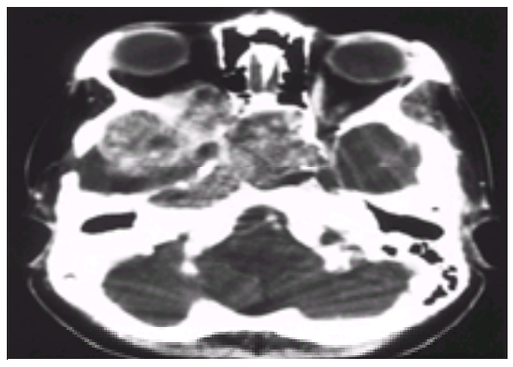

FIGURE 1-9. Computed tomography scan of the base of skull of a woman with proptosis and right-sided facial pain. There is extensive tumor erosion of the orbital wall, clivus, and the floor of the middle cranial fossa.

Orbital Syndrome

Orbital metastases usually present with progressive pain in the retro-orbital and supraorbital area of the affected eye. Blurred vision and diplopia may be associated complaints. Signs may include proptosis, chemosis of the involved eye, external ophthalmoparesis, ipsilateral papilledema, and decreased sensation in the ophthalmic division of the trigeminal nerve. Imaging with MRI or CT scan can delineate the extent of bony damage and orbital infiltration.

Parasellar Syndrome

The parasellar syndrome typically presents as unilateral supraorbital and frontal headache, which may be associated with diplopia (355). There may be ophthalmoparesis or papilledema, and formal visual field testing may demonstrate hemianopsia or quadrantanopsia.

Middle Cranial Fossa Syndrome

The middle cranial fossa syndrome presents with facial numbness, paresthesias, or pain, which is usually referred to the cheek or jaw (in the distribution of second or third divisions of the trigeminal nerve) (356). The pain is typically described as a dull continual ache, but may also be paroxysmal or lancinating. On examination, patients may have hypesthesia in the trigeminal nerve distribution and signs of weakness in the ipsilateral muscles of mastication. Occasionally patients have other neurological signs such as abducens palsy (353,357).

Jugular Foramen Syndrome

The jugular foramen syndrome usually presents with hoarseness or dysphagia. Pain is usually referred to the ipsilateral ear or mastoid region and may occasionally present as glossopharyngeal neuralgia, with or without syncope (353). Pain may also be referred to the ipsilateral neck or shoulder. Neurological signs include ipsilateral Horner's syndrome, and paresis of the palate, vocal cord, sternocleidomastoid, or trapezius. Ipsilateral paresis of the tongue may also occur if the tumor extends to the region of the hypoglossal canal.

Occipital Condyle Syndrome

The occipital condyle syndrome presents with unilateral occipital pain that is worsened with neck flexion (358,359). The patient may complain of neck stiffness. Pain intensity is variable but can be severe. Examination may reveal a head tilt, limited movement of the neck, and tenderness to palpation over the occipitonuchal junction. Neurological findings may include ipsilateral hypoglossal nerve paralysis and sternocleidomastoid weakness.

Clivus Syndrome

The clivus syndrome is characterized by vertex headache, which is often exacerbated by neck flexion. Lower cranial nerve (VI-XII) dysfunction follows and may become bilateral.

Sphenoid Sinus Syndrome

A sphenoid sinus metastasis often presents with bifrontal and/or retro-orbital pain, which may radiate to the temporal regions (360). There may be associated features of nasal congestion and diplopia. Physical examination is often unremarkable although unilateral or bilateral sixth-nerve paresis can be present.

Painful Cranial Neuralgias

As noted, specific cranial neuralgias can occur from metastases in the base of skull or leptomeninges. They are most commonly observed in patients with prostate and lung cancer (361). Invasion of the soft tissues of the head or neck, or involvement of sinuses can also eventuate in such lesions. Each of these syndromes has a characteristic presentation. Early diagnosis may allow effective treatment of the underlying lesion before progressive neurological injury occurs.

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia has been reported in patients with leptomeningeal metastases (340), the jugular foramen syndrome (353), or head and neck malignancies (362,363 and 364). This syndrome presents as severe pain in the throat or neck, which may radiate to the ear or mastoid region. Pain may be induced by swallowing. In some patients, pain is associated with sudden orthostasis and syncope.

Trigeminal Neuralgia

Trigeminal pains may be continual, paroxysmal, or lancinating. Pain that mimics classical trigeminal neuralgia can be induced by tumors in the middle or posterior fossa

(357,365,366 and 367) or leptomeningeal metastases (339). Continual pain in a trigeminal distribution may be an early sign of acoustic neuroma (368). All cancer patients who develop trigeminal neuralgia should be evaluated for the existence of an underlying neoplasm.

Ear and Eye Pain Syndromes

Otalgia

Otalgia is the sensation of pain in the ear. Referred otalgia is pain felt in the ear but originating from a nonotological source. The rich sensory innervation of the ear derives from four cranial nerves and two cervical nerves that also supply other areas in the head, neck, thorax, and abdomen. Pain referred to the ear may originate in areas far removed from the ear itself. Otalgia is reported among patients with carcinoma of the oropharynx or hypopharynx (369,370), acoustic neuroma (371), and metastases to the temporal bone or infratemporal fossa (372,373).

Eye Pain

Blurring of vision and eye pain are the two most common symptoms of choroidal metastases (374,375 and 376). More commonly chronic eye pain is related to metastases to the bony orbit, intraorbital structures such as the rectus muscles (377,378), or optic nerve (379).

Uncommon Causes of Headache and Facial Pain

Headache and facial pain in cancer patients may have many other causes. Unilateral facial pain can be the initial symptom of an ipsilateral lung tumor (380,381,382 and 383). Presumably this referred pain is mediated by vagal afferents. Facial squamous cell carcinoma of the skin may present with facial pain due to extensive perineural invasion (384). Patients with Hodgkin's disease may have transient episodes of neurological dysfunction that has been likened to migraine (385). Headache may occur with cerebral infarction or hemorrhage, which may be due to nonbacterial thrombotic endocarditis or disseminated intravascular coagulation. Headache is also the usual presentation of sagittal sinus occlusion, which may be due to tumor infiltration, hypercoagulable state, or treatment with L-asparaginase therapy (386). Headache due to pseudotumor cerebri has also been reported to be the presentation of SVC obstruction in a patient with lung cancer (387). Tumors of the sinonasal tract may present with deep facial or nasal pain (388).

Neuropathic Pains Involving the Peripheral Nervous System

Neuropathic pains involving the peripheral nervous system are common. The syndromes include painful radiculopathy, plexopathy, mononeuropathy, or peripheral neuropathy.

Painful Radiculopathy

Radiculopathy or polyradiculopathy may be caused by any process that compresses, distorts, or inflames nerve roots. Painful radiculopathy is an important presentation of epidural tumor and leptomeningeal metastases (see the section Leptomeningeal Metastases).

Postherpetic Neuralgia

Postherpetic neuralgia is defined solely by the persistence of pain in the region of a zoster infection. Although some authors apply this term if pain continues beyond lesion healing, most require a period of weeks to months before this label is used. A criterion of pain persisting beyond 2 months after lesion healing is recommended (205). One study suggests that postherpetic neuralgia is two to three times more frequent in the cancer population than the general population (204). In patients with postherpetic neuralgia and cancer, changes in the intensity or pattern of pain, or the development of new neurological deficits may indicate the possibility of local neoplasm and should be investigated.

Cervical Plexopathy

The ventral rami of the upper four cervical spinal nerves join to form the cervical plexus between the deep anterior and lateral muscles of the neck. Cutaneous branches emerge from the posterior border of the sternocleidomastoid. In the cancer population, plexus injury is frequently due to tumor infiltration or treatment (including surgery or radiotherapy) to neoplasms in this region (389). Tumor invasion or compression of the cervical plexus can be caused by direct extension of a primary head and neck malignancy or neoplastic (metastatic or lymphomatous) involvement of the cervical lymph nodes (389). Pain may be experienced in the preauricular (greater auricular nerve) or postauricular (lesser and greater occipital nerves) regions, or the anterior neck (transverse cutaneous and supraclavicular nerves). Pain may refer to the lateral aspect of the face or head, or to the ipsilateral shoulder. The overlap in the pain referral patterns from the face and neck may relate to the close anatomical relationship between the central connections of cervical afferents and the afferents carried in cranial nerves V, VII, IX, and X in the upper cervical spinal cord. The pain may be aching, burning, or lancinating, and is often exacerbated by neck movement or swallowing. Associated features can include ipsilateral Horner's syndrome or hemidiaphragmatic paralysis. The diagnosis must be distinguished from EC of the cervical spinal cord and leptomeningeal metastases. MRI or CT imaging of the neck and cervical spine is usually required to evaluate the etiology of the pain.

Brachial Plexopathy

The two most common causes of brachial plexopathy in cancer patients are tumor infiltration and radiation injury. Less common causes of painful brachial plexopathy include trauma during surgery or anesthesia, radiation-induced second neoplasms, acute brachial plexus ischemia, and paraneoplastic brachial neuritis.

Malignant Brachial Plexopathy

Plexus infiltration by tumor is the most prevalent cause of brachial plexopathy. Malignant brachial plexopathy is most common in patients with lymphoma, lung cancer, or breast cancer. The invading tumor usually arises from adjacent axillary, cervical, and supraclavicular lymph nodes (lymphoma and breast cancer) or from the lung (superior sulcus tumors or so-called Pancoast tumors) (390,391). Pain is nearly universal, occurring in 85% of patients, and often precedes neurological signs or symptoms by months (391). Lower plexus involvement (C7, C8, T1 distribution) is typical, and is reflected in the pain distribution, which usually involves the elbow, medial forearm and fourth and fifth fingers. Pain may sometimes localize to the posterior arm or elbow. Severe aching is usually reported, but patients may also experience constant or lancinating dysesthesias along the ulnar aspect of the forearm or hand.

Tumor infiltration of the upper plexus (C5–C6 distribution) is less common. This lesion is characterized by pain in the shoulder girdle, lateral arm and hand. Seventy-five percent of patients presenting with upper plexopathy subsequently develop a panplexopathy, and 25% of patients present with panplexopathy (390).

Cross-sectional imaging is essential in all patients with symptoms or signs compatible with plexopathy (Fig. 1-10). In one study, CT scanning had 80–90% sensitivity in detecting tumor infiltration (392). Others have demonstrated improved diagnostic yield with a multiplanar imaging technique (393). Although there are no comparative data on the sensitivity and specificity of CT and MRI in this setting, MRI does have the theoretical advantage of reliably assessing the integrity of the adjacent epidural space (394).

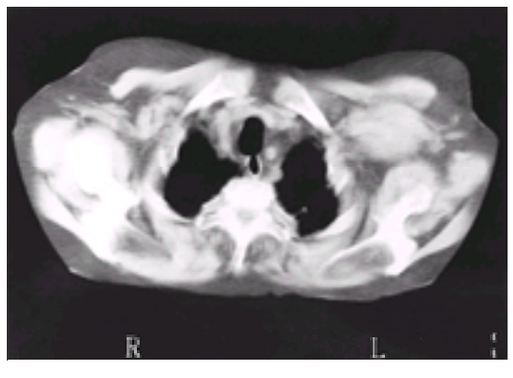

FIGURE 1-10. Contrast-enhanced computed tomography scan of the brachial plexus in a 64-year-old woman who has a past history of breast cancer and presents with

left arm and hand pain. There is a mass in the left brachial plexus. L, left; R, right.

Electrodiagnostic studies may be helpful in patients with suspected plexopathy particularly when neurological examination and imaging studies are normal (395). Although not specific for tumor, abnormalities on electromyography (EMG) or somatosensory evoked potentials may establish the diagnosis of plexopathy and thereby confirm the need for additional evaluation.

Patients with malignant brachial plexopathy are at high risk for epidural extension of the tumor (273,389). Epidural disease can occur as the neoplasm grows medially and invades vertebrae or tracks along nerve roots through the intervertebral foramina. In the latter case, there may be no evidence of bony erosion on imaging studies. The development of Horner's syndrome, evidence of panplexopathy, or finding of paraspinal tumor or vertebral damage on CT or MRI are highly associated with epidural extension and should lead to definitive imaging of the epidural tumor (273,389).

Radiation-Induced Brachial Plexopathy

Two distinct syndromes of radiation-induced brachial plexopathy have been described: (a) early onset transient plexopathy (see the section Early Onset Brachial Plexopathy) and, (b) delayed onset progressive plexopathy. Delayed onset progressive plexopathy can occur 6 months to 20 years after a course of radiotherapy that included the plexus in the radiation portal. In contrast to tumor infiltration, pain is a relatively uncommon presenting symptom (18%), and when present is usually less severe (390). Weakness and sensory changes predominate in the distribution of the upper plexus (C5, C6 distribution) (396,397 and 398). Radiation changes in the skin and lymphedema are commonly associated. The CT scan usually demonstrates diffuse infiltration that cannot be distinguished from tumor infiltration. There is no specific advantage to MRI scanning. In particular, increased T2 signal in or near the brachial plexus is commonly seen in both radiation plexopathy and tumor infiltration (394). EMG may demonstrate myokymia (396,399,400). Although a careful history, combined with neurological findings and the results of CT scanning and electrodiagnostic studies, can strongly suggest the diagnosis of radiation-induced injury, repeated assessments over time may be needed to confirm the diagnosis. Rare patients require surgical exploration of the plexus to exclude neoplasm and establish the etiology. When due to radiation, plexopathy is usually progressive (389,401), although some patients plateau for a variable period of time.

Uncommon Causes of Brachial Plexopathy

Malignant peripheral nerve tumor or a second primary tumor in a previously irradiated site can account for pain recurring late in the patient's course (402,403). Pain has been reported to occur as a result of brachial plexus entrapment in a lymphedematous shoulder (398), and as a consequence of acute ischemia many years after axillary radiotherapy (404). An idiopathic brachial plexopathy has also been described in patients with Hodgkin's disease (405).

Lumbosacral Plexopathy

The lumbar plexus, which lies in the paravertebral psoas muscle, is formed primarily by the ventral rami of L1-4. The sacral plexus forms in the sacroiliac notch from the ventral rami of S1-3 and the lumbosacral trunk (L4-5), which courses caudally over the sacral ala to join the plexus (406). Lumbosacral plexopathy may be associated with pain in the lower abdomen, inguinal region, buttock, or leg (407). In the cancer population, lumbosacral plexopathy is usually caused by neoplastic infiltration or compression. Radiation-induced plexopathy also occurs, and occasional patients develop the lesion as a result of surgical trauma, infarction, cytotoxic damage, infection in the pelvis or psoas muscle, abdominal aneurysm, or idiopathic lumbosacral neuritis. Polyradiculopathy from leptomeningeal metastases or epidural metastases can mimic lumbosacral plexopathy.

Malignant Lumbosacral Plexopathy

The primary tumors most frequently associated with malignant lumbosacral plexopathy include colorectal, cervical, breast, sarcoma, and lymphoma (389,407). Most tumors involve the plexus by direct extension from intrapelvic neoplasm. Metastases account for only one-fourth of cases. In one study, two-thirds of patients developed plexopathy within 3 years of their primary diagnosis and one-third presented within 1 year (407).

Pain is, typically, the first symptom and it is experienced by almost all patients at some point, and it is the only symptom in almost 20% of patients. The quality is aching, pressure-like, or stabbing; dysesthesias are relatively uncommon. Most patients develop numbness, paresthesias or weakness weeks to months after the pain begins. Common signs include leg weakness that involves multiple myotomes, sensory loss that crosses dermatomes, reflex asymmetry, focal tenderness, leg edema, and positive, direct, or reverse, straight-leg raising signs.

An upper plexopathy occurs in almost one-third of patients with lumbosacral plexopathy (407). This lesion is usually due to direct extension from a low abdominal tumor, most frequently colorectal. Pain may be experienced in the back, lower abdomen, flank, or iliac crest, or the anterolateral thigh. Examination may reveal sensory, motor and reflex changes in a L1-4 distribution. A subgroup of these patients presents with a syndrome characterized by pain and paresthesias limited to the lower abdomen or inguinal region, variable sensory loss and no motor findings. CT scan may show tumor adjacent to the L1 vertebra (the L1 syndrome) (407) or along the pelvic sidewall, where it presumably damages the ilioinguinal, iliohypogastric, or genitofemoral nerves. Another subgroup has neoplastic involvement of the psoas muscle and presents with a syndrome characterized by upper lumbosacral plexopathy, painful flexion of the ipsilateral hip, and positive psoas muscle stretch test. This has been termed the malignant psoas syndrome (408). Similarly, pain in the distribution of the femoral nerve has been observed in the setting of recurrent retroperitoneal sarcoma (409) and tumor in the iliac crest can compress the lateral cutaneous nerve of the thigh, producing a pain that mimics meralgia paresthetica (410).

A lower plexopathy occurs in just over 50% of patients with malignant lumbosacral plexopathy (407). This lesion is usually due to direct extension from a pelvic tumor, most frequently rectal cancer, gynecological tumors, or pelvic sarcoma. Pain may be localized in the buttocks and perineum, or referred to the posterolateral thigh and leg. Associated symptoms and signs conform to an L4–S1 distribution. Examination may reveal weakness or sensory changes in the L5 and S1 dermatomes and a depressed ankle jerk. Other findings include leg edema, bladder or bowel dysfunction, sacral or sciatic notch tenderness, and a positive, straight-leg raising test. A pelvic mass may be palpable.

Sacral plexopathy may occur from direct extension of a sacral lesion or a presacral mass. This may present with predominant involvement of the lumbosacral trunk, characterized by numbness over the dorsal medial foot and sole, and weakness of knee flexion, ankle dorsiflexion, and inversion. Other patients demonstrate particular involvement of the coccygeal plexus, with prominent sphincter dysfunction and perineal sensory loss. The latter syndrome occurs with low pelvic tumors such as those arising from the rectum or prostate.

A panplexopathy with involvement in a L1–S3 distribution occurs in almost one-fifth of patients with lumbosacral plexopathy (407). Local pain may occur in the lower abdomen, back, buttocks, or perineum. Referred pain can be experienced anywhere in distribution of the plexus. Leg edema is extremely common. Neurological deficits may be confluent or patchy within the L1–S3 distribution and a positive, straight-leg raising test is usually present.

Autonomic dysfunction, particularly anhydrosis and vasodilation, has been associated with plexus and peripheral nerve injuries. Focal autonomic neuropathy, which may suggest the anatomical localization of the lesion (411), has been reported as the presenting symptom of metastatic lumbosacral plexopathy (412).

Cross-sectional imaging, with either CT or MRI, is the preferred diagnostic procedure to evaluate lumbosacral plexopathy (Fig. 1-11). Scanning should be done from the level of the L1 vertebral body, through the sciatic notch. When using CT scanning techniques, images should include bone and soft-tissue windows. Limited data suggests superior sensitivity MRI over CT imaging (413). Definitive imaging of the epidural space adjacent to the plexus should be considered in the patient who has features indicative of a relatively high risk of epidural extension, including bilateral symptoms or signs, unexplained incontinence, or a prominent paraspinal mass (273,407).

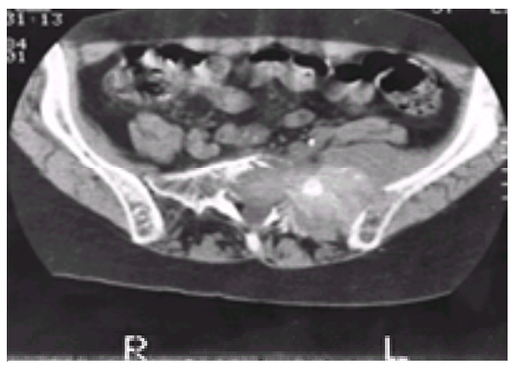

FIGURE 1-11. Computed tomography scan at the S1 level in a man with low back pain and pain radiating down the posterior aspect of the left leg. The scan shows a large mass invading the left sacrum with extension to the pelvic sidewall. L, left; R, right.

Radiation-Induced Lumbosacral Plexopathy

Radiation fibrosis of the lumbosacral plexus is a rare complication that may occur from 1 to over 30 years following radiation treatment. The use of intracavitary radium implants for carcinoma of the cervix may be an additional risk factor (414). Radiation-induced plexopathy typically presents with progressive weakness and leg swelling. Pain is not usually a prominent feature (414,415). Weakness typically begins distally in the L5–S1 segments and is slowly progressive. The symptoms and signs may be bilateral (415). If CT scanning demonstrates a lesion, it is usually a nonspecific diffuse infiltration of the tissues. EMG may show myokymic discharges (415).

Uncommon Causes of Lumbosacral Plexopathy

Lumbosacral plexopathy may occur following intraarterial cisplatinum infusion and embolization techniques. This syndrome has been observed following attempted embolization of a bleeding rectal lesion. Benign conditions that may produce similar findings include hemorrhage or abscess in the iliopsoas muscle (406), abdominal aortic aneurysms, diabetic radiculoplexopathy, vasculitis, and an idiopathic lumbosacral plexitis analogous to acute brachial neuritis (406).

Painful Mononeuropathy

Tumor-Related Mononeuropathy

Tumor-related mononeuropathy usually results from compression or infiltration of a nerve from tumor arising in an adjacent bony structure. The most common example of this phenomenon is intercostal nerve injury in a patient with rib metastases. Constant burning pain and other dysesthesias in the area of sensory loss are the typical clinical presentation. Other examples include the cranial neuralgias previously described, sciatica associated with tumor invasion of the sciatic notch, and common peroneal nerve palsy associated with primary bone tumors of the proximal fibula and lateral cutaneous nerve of the thigh neuralgia associated with iliac crest tumors.

Other Causes of Mononeuropathy

Cancer patients also develop mononeuropathies from many other causes. Postsurgical syndromes are well described (see the section Chronic Post Pain Syndormes) and radiation injury of a peripheral nerve occurs occasionally. Rarely cancer patients develop nerve entrapment syndromes (such as carpal tunnel syndrome) related to edema or direct compression by tumor (416).

Painful Peripheral Neuropathies

Painful peripheral neuropathies have multiple causes, including nutritional deficiencies, other metabolic derangements (e.g., diabetes and renal dysfunction), neurotoxic effects of chemotherapy, and, rarely, paraneoplastic syndromes.

Toxic Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy is a common problem, which is typically manifested by painful paresthesias in the hands and/or feet, and signs consistent with an axonopathy, including “stocking-glove” sensory loss, weakness, hyporeflexia, and autonomic dysfunction (417). The pain is usually characterized by continuous burning or lancinating pains, either of which may be increased by contact. The drugs most commonly associated with a peripheral neuropathy are the vinca alkaloids (especially vincristine) (142,418), cisplatinum (419,420), and oxaliplatin (421). Procarbazine, carboplatinum, misonidazole, and hexamethylmelamine have also been implicated as causes for this syndrome (146,422). Data from several studies indicates that the risk of neuropathy associated with cisplatinum can be diminished by the coadministration of the radioprotective agent amifostine at the time of treatment (423).

Paraneoplastic Painful Peripheral Neuropathy

Paraneoplastic painful peripheral neuropathy can be related to injury to the dorsal root ganglion (also known as *subacute sensory neuronopathy* or *ganglionopathy*) or injury to peripheral nerves (424). These syndromes may be the initial manifestation of an underlying malignancy. Except for the neuropathy associated with myeloma (425,426), their course is usually independent of the primary tumor (424,427).

Subacute sensory neuronopathy is characterized by pain (usually dysesthetic), paresthesias, sensory loss in the extremities, and severe sensory ataxia (428). Although it is usually associated with small cell carcinoma of the lung (429), other tumor types, including breast cancer (430), Hodgkin's disease (431), and varied solid tumors, are rarely associated. Both constant and lancinating dysesthesias occur and typically predate other symptoms. Neuropathic symptoms (pain, paresthesia, sensory loss) were asymmetric at onset, with a predilection for the upper limbs. Indeed, in one instance a painful bilateral ulnar neuropathy is described (432). The pain usually develops before the tumor is evident and its course is typically independent. Coexisting autonomic, cerebellar, or cerebral abnormalities are common (428). The syndrome, which results from an inflammatory process involving the dorsal root ganglia, may be part of a more diffuse autoimmune disorder that can affect the limbic region, brainstem, and spinal cord (427,428,433). An antineuronal IgG antibody (“anti-Hu”), which recognizes a low molecular weight protein present in most small cell lung carcinomas, has been associated with the condition (427).

A sensorimotor peripheral neuropathy, which may be painful, has been observed in association with diverse neoplasms, particularly Hodgkin's disease and paraproteinemias (427,428). The peripheral neuropathies associated with multiple myeloma, Waldenström's macroglobulinemia, small-fiber amyloid neuropathy, and osteosclerotic myeloma, are thought to be due to antibodies that cross-react with constituents of peripheral nerves (426). Clinically evident peripheral neuropathy occurs in approximately 15% of patients with multiple myeloma, and electrophysiologic evidence of this lesion can be found in 40% (426). The pathophysiology of the neuropathy is unknown.

Pain Syndromes of the Viscera and Miscellaneous Tumor-Related Syndromes

Pain may be caused by pathology involving the luminal organs of the gastrointestinal or genitourinary tracts, the parenchymal organs, the peritoneum, or the retroperitoneal soft tissues. Obstruction of hollow viscus, including intestine, biliary tract, and ureter, produces visceral nociceptive syndromes that are well described in the surgical literature (434). Pain arising from retroperitoneal and pelvic lesions may involve mixed nociceptive and neuropathic mechanisms if both somatic structures and nerves are involved.

Hepatic Distention Syndrome

Pain sensitive structures in the region of the liver include the liver capsule, blood vessels, and biliary tract (435). Nociceptive afferents that innervate these structures travel via the celiac plexus, the phrenic nerve, and the lower right intercostal nerves. Extensive intrahepatic metastases, or gross hepatomegaly associated with cholestasis, may produce discomfort in the right subcostal region, and less commonly in the right mid-back or flank (435,436 and 437). Referred pain may be experienced in the right neck or shoulder, or in the region of the right scapula (436). The pain, usually described as a dull aching, may be exacerbated by movement, pressure in the abdomen, and deep inspiration. Pain is commonly accompanied by symptoms of anorexia and nausea. Physical examination may reveal a hard

irregular subcostal mass that descends with respiration and is dull to percussion. Other features of hepatic failure may be present. Imaging of the hepatic parenchyma by either ultrasound or CT will usually identify the presence of space-occupying lesions or cholestasis (Fig. 1-12).

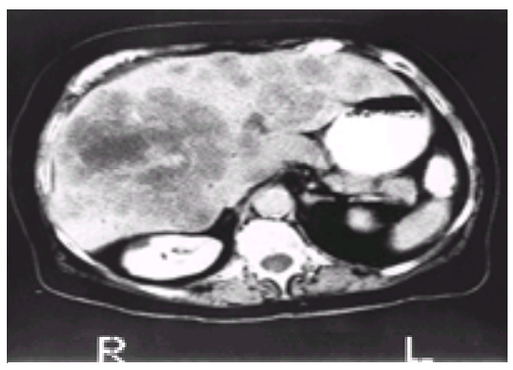

FIGURE 1-12. Computed tomography scan of the abdomen of a 72-year-old man with metastatic colon cancer and persistent, right, upper-quadrant abdominal pain. The scan demonstrates extensive liver metastases. L, left; R, right.

Occasional patients who experience chronic pain due to hepatic distention develop an acute intercurrent subcostal pain that may be exacerbated by respiration. Physical examination may demonstrate a palpable or audible rub. These findings suggest the development of an overlying peritonitis, which can develop in response to some acute event, such as a hemorrhage into a metastasis.

Midline Retroperitoneal Syndrome

Retroperitoneal pathology involving the upper abdomen may produce pain by injury to deep somatic structures of the posterior abdominal wall, distortion of pain sensitive connective tissue, vascular and ductal structures, local inflammation, and direct infiltration of the celiac plexus. The most common causes are pancreatic cancer (438,439 and 440) and retroperitoneal lymphadenopathy (441,442 and 443), particularly celiac lymphadenopathy (444). The reasons for the high frequency of perineural invasion and the presence of pain in pancreatic cancer may be related to locoregional secretion and activation of growth factor and its high-affinity receptor TrkA. These factors are involved in stimulating epithelial cancer cell growth and perineural invasion (445). In some instances of pancreatic cancer, obstruction of the main pancreatic duct with subsequent ductal hypertension generates pain which can be relieved by stenting of the pancreatic duct (446). The pain is experienced in the epigastrium, in the low thoracic region of the back, or in both locations. It is often diffuse and poorly localized. It is usually dull and boring in character, exacerbated with recumbency, and improved by sitting. The lesion can usually be demonstrated by CT, MRI, or ultrasound scanning of the upper abdomen (Fig. 1-13). If tumor is identified in the paravertebral space, or vertebral body destruction is identified, consideration should be given to careful evaluation of the epidural space (273).

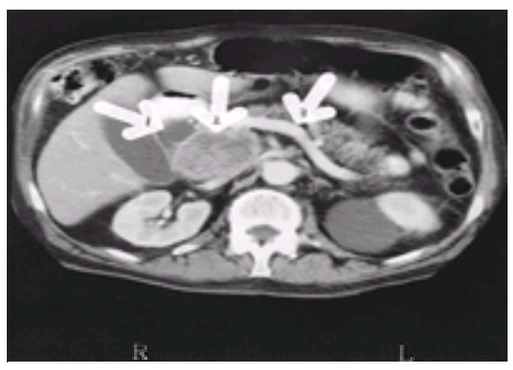

FIGURE 1-13. Computed tomography scan of the abdomen of a 47-year-old woman with epigastric pain and jaundice. The computed tomography shows a large mass in the head of the pancreas (*arrow 2*), dilatation of the common bile duct (*arrow 1*), and dilatation of the pancreatic duct (*arrow 3*). L, left; R, right.

Chronic Intestinal Obstruction

Abdominal pain is an almost invariable manifestation of chronic intestinal obstruction, which may occur in patients with abdominal or pelvic cancers (447,448). The factors that contribute to this pain include smooth muscle contractions, mesenteric tension and mural ischemia. Obstructive symptoms may be due primarily to the tumor, or more likely, to a combination of mechanical obstruction and other processes such as autonomic neuropathy and ileus from metabolic derangements or drugs. Both continuous and colicky pains occur which may be referred to the dermatomes represented by the spinal segments supplying the affected viscera. Vomiting, anorexia, and constipation are important associated symptoms.

Peritoneal Carcinomatosis

Peritoneal carcinomatosis occurs most often by transcelomic spread of abdominal or pelvic tumor. Excepting breast cancer, hematogenous spread of an extraabdominal neoplasm in this pattern is rare. Carcinomatosis can cause peritoneal inflammation, mesenteric tethering, malignant adhesions, and ascites, all of which can cause pain. Pain and abdominal distention are the most common presenting symptoms. Mesenteric tethering and tension appears to cause a diffuse abdominal or low back pain. Tense malignant ascites can produce diffuse abdominal discomfort and a distinct stretching pain in the anterior abdominal wall. Adhesions can also cause obstruction of hollow viscus, with intermittent colicky pain (449). CT scanning may demonstrate evidence of ascites, omental infiltration, and peritoneal nodules (450) (Fig. 1-14).

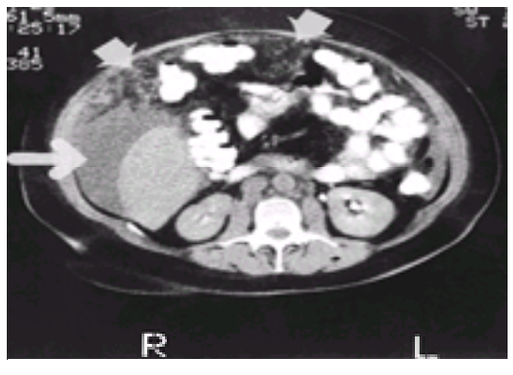

FIGURE 1-14. Computed tomography scan of the abdomen of a 66-year-old woman with stage IV ovarian cancer. The short arrows indicate areas of peritoneal thickening and infiltration. The large horizontal arrow indicates ascitic fluid interposed lateral to the lower lobe of the liver. L, left; R, right.

Malignant Perineal Pain

Tumors of the colon or rectum, female reproductive tract, and distal genitourinary system are most commonly responsible for perineal pain (451,452,453,454 and 455).

Severe perineal pain following antineoplastic therapy may precede evidence of detectable disease and should be viewed as a potential harbinger of progressive or recurrent cancer (451,452,455). There is evidence to suggest that this phenomenon is caused by microscopic perineural invasion by recurrent disease (456). The pain, which is typically described as constant and aching, is often aggravated by sitting or standing, and may be associated with tenesmus or bladder spasms (451).

Tumor invasion of the musculature of the deep pelvis can also result in a syndrome that appears similar to the so-called “tension myalgia of the pelvic floor” (457). The pain is typically described as a constant ache or heaviness that exacerbates with upright posture. When due to tumor, the pain may be concurrent with other types of perineal pain. Digital examination of the pelvic floor may reveal local tenderness or palpable tumor.

Adrenal Pain Syndrome

Large adrenal metastases, common in lung cancer, may produce unilateral flank pain, and less commonly, abdominal pain. Pain is of variable severity, and it can be severe (458).

Ureteric Obstruction

Ureteric obstruction is most frequently caused by tumor compression or infiltration within the true pelvis (459,460). Less commonly, obstruction can be more proximal, associated with retroperitoneal lymphadenopathy, an isolated retroperitoneal metastasis, mural metastases, or intraluminal metastases. Cancers of the cervix, ovary, prostate, and rectum are most commonly associated with this complication. Nonmalignant causes, including retroperitoneal fibrosis resulting from radiotherapy or graft-versus-host disease, occur rarely (461,462 and 463).

Pain may or may not accompany ureteric obstruction. When present, it is typically a dull chronic discomfort in the flank, with radiation into the inguinal region or genitalia. If pain does not occur, ureteric obstruction may be discovered when hydronephrosis is discerned on abdominal imaging procedures or renal failure develops. Ureteric obstruction can be complicated by pyelonephritis or pyonephrosis, which often present with features of sepsis, loin pain, and dysuria. Diagnosis of ureteric obstruction can usually be confirmed by the demonstration of hydronephrosis on renal sonography. The level of obstruction can be identified by pyelography. CT scanning techniques will usually demonstrate the cause (464).

Ovarian Cancer Pain

Moderate to severe chronic abdominopelvic pain is the most common symptom of ovarian cancer. It is reported by almost two-thirds of patients in the 2 weeks prior to the onset or recurrence of the disease (3). In patients who have been previously treated, it is an important symptom of potential recurrence (3).

Lung Cancer Pain

Even in the absence of involvement of the chest wall or parietal pleura, lung tumors can produce a visceral pain syndrome. In a large case series of lung cancer patients, pain was unilateral in 80% of the cases and bilateral in 20%. Among patients with hilar tumors, the pain was reported to the sternum or the scapula. Upper and lower lobe tumors referred to the shoulder and to the lower chest respectively (465,466). As previously mentioned (see the section Uncommon Causes of Headache and Facial Pain), early lung cancers can generate ipsilateral facial pain (380,381,383,467). It is postulated that this pain syndrome is generated via vagal afferent neurones.

Other Uncommon Visceral Pain Syndromes

Sudden onset severe abdominal or loin pain may be caused by nontraumatic rupture of a visceral tumor. This has been most frequently reported with hepatocellular cancer (468). Kidney rupture due to a renal metastasis from an adenocarcinoma of the colon (469) and metastasis-induced perforated appendicitis (470) have been reported. Torsion of pedunculated visceral tumors can produce a cramping abdominal pain (471,472 and 473).

Paraneoplastic Nociceptive Pain Syndromes

Tumor-Related Gynecomastia

Tumors that secrete chorionic gonadotrophin, including malignant and benign tumors of the testis (474,475,476 and 477) and rarely cancers from other sites (478,479), may be associated with chronic breast tenderness or gynecomastia. Approximately 10% of patients with testis cancer have gynecomastia or breast tenderness at presentation, and the likelihood of gynecomastia is greater with increasing chorionic gonadotrophin level (477). Breast pain can be the first presentation of an occult tumor (474,475 and 476).

Paraneoplastic Pemphigus

Paraneoplastic pemphigus is a rare mucocutaneous disorder associated with non-Hodgkin's lymphoma; chronic lymphocytic leukemia. The condition is characterized by widespread shallow ulcers with hemorrhagic crusting of the lips, conjunctival bullae, and, uncommonly, pulmonary lesions. Characteristically, histopathology reveals intraepithelial and subepithelial clefting and immunoprecipitation studies reveal autoantibodies directed against desmoplakins and desmogleins (480,481).

Chronic Pain Syndromes Associated with Cancer Therapy

Most treatment-related pains are caused by tissue-damaging procedures. These pains are acute, predictable, and self-limited. Chronic, treatment-related pain syndromes are associated with either a persistent nociceptive complication of an invasive treatment (such as a postsurgical abscess), or more commonly, neural injury. In some cases, these syndromes occur long after the therapy is completed, resulting in a difficult differential diagnosis between recurrent disease and a complication of therapy.

Postchemotherapy Pain Syndromes

Chronic Painful Peripheral Neuropathy

Although most patients who develop painful peripheral neuropathy due to cytotoxic therapy gradually improve, some develop a persistent pain. In particular, peripheral neuropathy associated with cisplatinum may continue to progress months after discontinuation of therapy and may persist for months to years (482,483). This is less common with vincristine or paclitaxel (484). The characteristics of this pain syndrome were described previously (see the section Toxic Peripheral Neuropathy).

Avascular (Aseptic) Necrosis of Femoral or Humeral Head

Avascular necrosis of the femoral or humeral head may occur either spontaneously or as a complication of intermittent or continuous corticosteroid therapy (485,486). Osteonecrosis may be unilateral or bilateral. Involvement of the femoral head is most common and typically causes pain in the hip, thigh, or knee. Involvement of the humeral head usually presents as pain in the shoulder, upper arm, or elbow. Pain is exacerbated by movement and relieved by rest. There may be local tenderness over the joint, but this is not universal. Pain usually precedes radiological changes by weeks to months; bone scintigraphy and MRI are sensitive and complementary diagnostic procedures. Early treatment consists of analgesics, decrease or discontinuation of steroids, and sometimes surgery. With progressive bone destruction, joint replacement may be necessary.

Plexopathy

Lumbosacral or brachial plexopathy may follow cisplatinum infusion into the iliac artery (487) or axillary artery (488), respectively. Affected patients develop pain, weakness, and paresthesias within 48 hours of the infusion. The mechanism for this syndrome is thought to be due to small vessel damage and infarction of the plexus or nerve. The prognosis for neurological recovery is not known.

Raynaud's Phenomenon

Among patients with germ cell tumors treated with cisplatin, vinblastine, and bleomycin, persistent Raynaud's phenomenon is observed in 20–30% of cases (170,489).

This effect has also been observed in patients with carcinoma of the head and neck treated with a combination of cisplatin, vincristine, and bleomycin (490). Pathophysiological studies have demonstrated that a hyperreactivity in the central sympathetic nervous system results in a reduced function of the smooth muscle cells in the terminal arterioles (491).

Chronic Pain Associated with Hormonal Therapy

Gynecomastia with Hormonal Therapy for Prostate Cancer

Chronic gynecomastia and breast tenderness are common complications of antiandrogen therapies for prostate cancer. The incidence of this syndrome varies among drugs. It is frequently associated with diethylstilbestrol (492) and bicalutamide (493), less commonly with flutamide (494) and cyproterone (495), and uncommonly among patients receiving LRF agonist therapy (175,176). Gynecomastia in the elderly must be distinguished from primary breast cancer or a secondary cancer in the breast (496,497).

Chronic Postsurgical Pain Syndromes

Surgical incision at virtually any location may result in chronic pain. Although persistent pain is occasionally encountered after nephrectomy, sternotomy, craniotomy, inguinal dissection, and other procedures, these pain syndromes are not well described in the cancer population. In contrast, several syndromes are now clearly recognized as sequelae of specific surgical procedures. The predominant underlying pain mechanism in these syndromes is neuropathic, resulting from injury to peripheral nerves or plexus.

Breast Surgery Pain Syndromes

Chronic pain of variable severity is a common sequel of surgery for breast cancer. In two large surveys, pain, paresthesias, and strange sensations were reported by 30–50% of the patients (498,499,500 and 501). The most common sites of pain were the breast scar region and the ipsilateral arm. Pain was more common among women who underwent breast conserving treatments than those who underwent mastectomy. The highest incidence of pain was reported by patients who had had both radio- and chemotherapy (499). Data from a retrospective survey of 408 mastectomy patients revealed that this phenomenon was more common among younger patients and that the pain severity attenuated over time (500).

Although chronic pain has been reported to occur after almost any surgical procedure on the breast (from lumpectomy to radical mastectomy), it is most common after procedures involving axillary dissection (398,502,503 and 504). Pain may begin immediately or as late as many months following surgery. The natural history of this condition appears to be variable, and both subacute and chronic courses are possible (505). The onset of pain later than 18 months following surgery is unusual, and a careful evaluation to exclude recurrent chest wall disease is recommended in this setting.

Postmastectomy pain is characterized as a constricting and burning discomfort localized to the medial arm, axilla, and anterior chest wall (504,506,507,508 and 509). On examination there is often an area of sensory loss within the region of the pain (508). The etiology is believed to be related to damage to the intercostobrachial nerve, a cutaneous sensory branch of Tl,2,3 (504,508). There is marked anatomical variation in the size and distribution of the intercostobrachial nerve and this may account for some of the variability in the distribution of pain observed in patients with this condition (510).

In some cases of pain after breast surgery, a trigger point can be palpated in the axilla or chest wall. The patient may restrict movement of the arm leading to frozen shoulder as a secondary complication.

Postradical Neck Dissection Pain

Long-standing locoregional pain after radical neck dissection is uncommon (511). Several types of postradical neck dissection pain are recognized. A persistent neuropathic pain can develop weeks to months after surgical injury to the cervical plexus. Tightness, along with burning or lancinating dysesthesias in the area of the sensory loss, are the characteristic symptoms. More commonly, chronic pain can result from musculoskeletal imbalance in the shoulder girdle following surgical removal of neck muscles (511). Similar to the droopy shoulder syndrome (512), this syndrome can be complicated by development of a thoracic outlet syndrome or suprascapular nerve entrapment, with selective weakness and wasting of the supraspinatus and infraspinatus muscles (513). Data from a large survey demonstrated that neck dissections sparing CN XI, and not dissecting level V of the neck when CN XI is spared, are associated with less shoulder and neck pain (514).

Escalating pain in patients who have undergone radical neck dissection may signify recurrent tumor or soft-tissue infection. These lesions may be difficult to diagnose in tissues damaged by radiation and surgery. Repeated CT or MRI scanning may be needed to exclude tumor recurrence. Empiric treatment with antibiotics should be considered (515,516).

Postthoracotomy Pain

There have been two major studies of postthoracotomy pain (517,518). In the first (518), three groups were identified: The largest (63%) had prolonged postoperative pain that abated within 2 months after surgery. Recurrent pain, following resolution of the postoperative pain, was usually due to neoplasm. A second group (16%) experienced pain that persisted following the thoracotomy, then increased in intensity during the follow-up period. Local recurrence of disease and infection were the most common causes of the increasing pain. A final group had a prolonged period of stable or decreasing pain that gradually resolved over a maximum 8-month period. This pain was not associated with tumor recurrence. Overall, the development of late or increasing postthoracotomy pain was due to recurrent or persistent tumor in greater than 95% of patients. This finding was corroborated in the more recent study that evaluated the records of 238 consecutive patients who underwent thoracotomy which identified recurrent pain in 20 patients. All were found to have tumor regrowth (517).

Patients with recurrent or increasing postthoracotomy pain should be carefully evaluated, preferably with a chest CT scan (Fig. 1-15) or MRI. Chest radiographs are insufficient to evaluate recurrent chest disease. In some patients, postthoracotomy pain appears to be caused by a taut muscular band within the scapular region. In such cases, pain may be amenable to trigger point injection of local anesthetic (519).

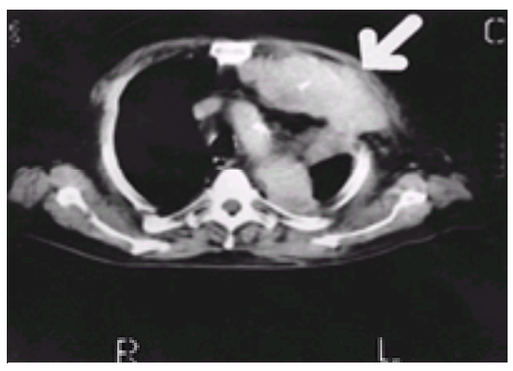

FIGURE 1-15. Chest computed tomography scan of a 55-yearold man who had recurrent left-sided chest wall pain 9 months after right upper lobectomy for squamous cell carcinoma of the lung. There is a chest wall recurrence associated with rib destruction and soft-tissue mass (*arrow*).

Postoperative Frozen Shoulder

Patients with postthoracotomy or postmastectomy pain are at risk for the development of a frozen shoulder (502). This lesion may become an independent focus of pain, particularly if complicated by RSD. Adequate postoperative analgesia and active mobilization of the joint soon after surgery are necessary to prevent these problems.

Phantom Pain Syndromes

Phantom limb pain is perceived to arise from an amputated limb, as if the limb were still contiguous with the body. Phantom pain is experienced by 60–80% of patients following limb amputation but is only severe in about 5–10% of cases (520,521). The incidence of phantom pain is significantly higher in patients with a long duration of preamputation pain and those with pain on the day before amputation (522,523). Patients who had pain prior to the amputation may experience phantom pain that replicates the earlier one (524). Phantom pain is more prevalent after tumor-related than traumatic amputations, and postoperative chemotherapy is an additional risk factor (525). The pain may be continuous or paroxysmal and is often associated with bothersome paresthesias. The phantom limb may assume painful and unusual postures and may gradually telescope and approach the stump. Phantom pain may initially magnify and then slowly fade over time. There is growing evidence that preoperative or postoperative neural blockade reduces the incidence of phantom limb pain during the first year after amputation (526,527,528 and 529).

Some patients have spontaneous partial remission of the pain. The recurrence of pain after such a remission, or the late onset of pain in a previously painless phantom limb, suggests the appearance of a more proximal lesion, including recurrent neoplasm (530).

Phantom pain syndromes have also been described after other surgical procedures. Phantom breast pain after mastectomy, which occurs in 15–30% of patients (498,531,532), also appears to be related to the presence of preoperative pain (532). The pain tends to start in the region of the nipple and then spread to the entire breast. The character of the pain is variable and may be lancinating, continuous, or intermittent (532). A phantom anus pain syndrome occurs in approximately 15% of patients who undergo abdominoperineal resection of the rectum (452,533). Phantom anus pain may develop either in the early postoperative period or after a latency of months to years. Late onset pain is almost always associated with tumor recurrence (452,533). Rare cases of phantom bladder pain after cystectomy (534) and phantom eye pain after enucleation (535,536) have also been reported.

Stump Pain

Stump pain occurs at the site of the surgical scar several months to years following amputation (537). It is usually the result of neuroma development at a site of nerve transection. This pain is characterized by burning or lancinating dysesthesias, which are often exacerbated by movement or pressure and blocked by an injection of a local anesthetic.

Postsurgical Pelvic Floor Myalgia

Surgical trauma to the pelvic floor can cause a residual pelvic floor myalgia, which like the neoplastic syndrome described previously (see the section Malignant Perineal Pain) mimics so-called tension myalgia (457). The risk of disease recurrence associated with this condition is not known, and its natural history has not been defined. In patients who have undergone anorectal resection, this condition must be differentiated from the phantom anus syndrome (see the section Phantom Pain Syndrome).

Chronic Postradiation Pain Syndromes

Chronic pain complicating radiation therapy tends to occur late in the course of a patient's illness. These syndromes must always be differentiated from recurrent tumor.

Radiation-Induced Brachial and Lumbosacral Plexopathies

Radiation-induced brachial and lumbosacral plexopathies were described previously (see the sections Brachial Plexopathy and Lumbosacral Plexopathy).

Chronic Radiation Myelopathy

Chronic radiation myelopathy is a late complication of spinal cord irradiation. The latency is highly variable but is most commonly 12–14 months. The most common presentation is a partial transverse myelopathy at the cervicothoracic level, sometimes in a Brown-Sequard pattern (538). Sensory symptoms, including pain, typically precede the development of progressive motor and autonomic dysfunction (538). The pain is characterized as a burning dysesthesia localized to the area of spinal cord damage or below. Imaging studies, particularly MRI, are important to exclude an epidural metastasis and demonstrate the nature and extent of intrinsic cord pathology, which may include atrophy, swelling, or syrinx. On MRI the signs of radiation myelitis include high-intensity signals on T2-weighted images or gadolinium enhancement of T1-weighted images (539,540). The course of chronic radiation myelopathy is characterized by steady progression over months, followed by a subsequent phase of slow progression or stabilization.

Chronic Radiation Enteritis and Proctitis

Chronic enteritis and proctocolitis occur as a delayed complication in 2–10% of patients who undergo abdominal or pelvic radiation therapy (197,541). The rectum and rectosigmoid are more commonly involved than the small bowel, a pattern that may relate to the retroperitoneal fixation of the former structures. The latency is variable (3 months–30 years) (197,541). Chronic radiation injury to the rectum can present as proctitis (with bloody diarrhea, tenesmus, and cramping pain), obstruction due to stricture formation, or fistulae to the bladder or vagina. Small bowel radiation damage typically causes colicky abdominal pain, which can be associated with chronic nausea or malabsorption. Barium studies may demonstrate a narrow tubular bowel segment resembling Crohn's disease or ischemic colitis. Endoscopy and biopsy may be necessary to distinguish suspicious lesions from recurrent cancer.

Radiation Cystitis

Radiation therapy used in the treatment of tumors of the pelvic organs (prostate, bladder, colon/rectum, uterus, ovary, and vagina/vulva) may produce a chronic radiation cystitis (542,543 and 544). The late sequelae of radiation injury to the bladder can range from minor temporary irritative voiding symptoms and asymptomatic hematuria to more severe complications such as gross hematuria, contracted nonfunctional bladder, persistent incontinence, and fistula formation. The clinical presentation can include frequency, urgency, dysuria, hematuria, incontinence, hydronephrosis, pneumaturia, and fecaluria.

Lymphedema Pain

One-third of patients with lymphedema as a complication of breast cancer or its treatment experience pain and tightness in the arm (545). Some patients develop nerve entrapment syndromes of the carpal tunnel syndrome or brachial plexus (398,546). Severe or increasing pain in a lymphedematous arm is strongly suggestive of tumor invasion of the brachial plexus (390,391).

Burning Perineum Syndrome

Persistent perineal discomfort is an uncommon delayed complication of pelvic radiotherapy. After a latency of 6–18 months, burning pain can develop in the perianal region; the pain may extend anteriorly to involve the vagina or scrotum (547). In patients who have had abdominoperineal resection, phantom anus pain and recurrent tumor are major differential diagnoses.

Osteoradionecrosis

Osteoradionecrosis is another late complication of radiotherapy. Bone necrosis, which occurs as a result of end-arteritis obliterans, may produce focal pain. Overlying tissue breakdown can occur spontaneously or as a result of trauma such as dental extraction or denture trauma (548,549). Delayed development of a painful ulcer must be differentiated from tumor recurrence.

Breakthrough Pain

Transitory exacerbations of severe pain over a baseline of moderate pain or less may be described as “breakthrough pain” (550). Breakthrough pains are common in both acute or chronic pain states. These exacerbations may be precipitated by volitional actions of the patient (so-called incident pains) such as movement, micturition, cough, or defecation, or by nonvolitional events such as bowel distention. Spontaneous fluctuations in pain intensity can also occur without an identifiable precipitant.

Breakthrough pains must be distinguished from exacerbations of pain associated with failure of analgesia. “End-of-dose failure (of analgesia)” is commonly observed as therapeutic levels of analgesic fall. This phenomena is observed most commonly when the interval between scheduled doses exceeds the known duration of action of short half-life analgesics. Because there is substantial interindividual differences in drug metabolism and excretion, some analgesics which may typically have a 4-hour duration of action, may be effective for only 2–3 hours in some individuals. Similarly, variability in the duration of analgesic effect is observed with long-acting

formulations such as oral morphine or transdermal fentanyl. End-of-dose failure is addressed through either dose or schedule modification.

In a survey by Portenoy and Hagen (550) of 63 cancer patients with pain requiring opioid analgesics, 41 (64%) reported breakthrough pain. Patients had a median of four episodes per day, the duration of which ranged seconds to hours (median/range: 30 min/1–240 min). Pain characteristics were extremely varied. Twenty-two (43%) pains were paroxysmal in onset; the remainder were more gradual and 21 (41%) were both paroxysmal and brief (lancinating pain). Fifteen (29%) of the pains were related to end-of-dose failure from a fixed dose of opioid on a regular schedule. Twenty-eight (55%) of the pains were precipitated; of these, 22 were caused by an action of the patient (incident pain), and six were associated with a nonvolitional precipitant such as flatulence. The pathophysiology of the pain was believed to be somatic in 17 (33%), visceral in 10 (20%), neuropathic in 14 (27%), and mixed in 10 (20%). Pain was related to the tumor in 42 (82%), the effects of therapy in seven (14%), and neither in two (4%). Diverse interventions were employed to manage these pains, with variable efficacy. In a study of 194 cancer patients with pain, Jacobsen (551) reported that 61% reported one or more episodes of breakthrough pain. These episodes were typically paroxysmal (56%), predictable (63%), and precipitated by patient action (67%). They had a mean duration of 20 minutes (range, 5 seconds–1.5 hours) and occurred an average of ten times per day (range, 1–80). In a survey of 22 hospice patients by Fine (552), 86% reported breakthrough pain, with an average of 2.9 episodes per 24-hour period and a mean pain intensity of seven on a 10-point scale. These episodes lasted an average of 52 minutes (range, 1–240). The range of time to relief of breakthrough pains was 5–60 minutes, with a mean of 30 minutes.

Syndromes of Breakthrough Pain

Pain exacerbations represent a heterogeneous phenomenon. The clinical approach to these problems is influenced by the specific underlying mechanism. It is useful, therefore, to define the specific breakthrough pain syndrome.

- Somatic movement-related pain (volitional and nonvolitional)
- Somatic nonmovement-related pain
- Neuropathic movement-related pain
- Neuropathic nonmovement-related pain
- Visceral pains—volitional
- Visceral pains—nonvolitional

Somatic, Movement-Related Breakthrough Pain

Volitional. This is the most common mechanism of breakthrough pain. It is most commonly observed when the pain associated with skeletal metastases is exacerbated by movement. This is particularly common when the axial skeleton and weight-bearing bones are involved; these episodes are generally predictable. The site of disease involvement influences which volitional movement produces pain. Thus the pain associated with vertebral, pelvic, or femoral metastases may be exacerbated by walking. The pain of shoulder girdle or humeral metastases my be exacerbated by reaching or lifting. The pain of rib metastases may be exacerbated by deep breathing. Often this sort of breakthrough pain may be prevented or modified by preemptive analgesia, orthotics, bone stabilization, or movement modification.

Nonvolitional. Nonvolitional movements, such as laughing, sneezing, coughing, or myoclonus, may also exacerbate skeletal pain. The spontaneous and nonpredictable nature of these episodes commonly precludes preemptive analgesia and management must address the possibility of reducing the frequency of the nonvolitional precipitant.

Somatic, Nonmovement-Related Breakthrough Pain

Occasionally, somatic structures can spontaneously produce transient exacerbation of pain unrelated to movement. In the setting of cancer pain, this is a relatively uncommon phenomenon. The best recognized syndrome is that of muscle cramps (322,323). Muscle cramps involve a focal transient exacerbation of pain related to a change in muscle tone, but without necessarily involving movement.

Neuropathic, Movement-Related Breakthrough Pain

Neuropathic pains are common among patients. Because of the proximity of neural and somatic structures, neuropathic pains are often exacerbated by volitional or nonvolitional movement.

Volitional. Neuropathic pain associated with compression of neural structures, such as the brachial plexus, lumbosacral plexus, spinal cord, and nerve roots, are commonly exacerbated by specific volitional activities. Indeed, these associations are often important in the clinical diagnosis. For example, back pain that is exacerbated by lying suggests EC of the cord or nerve roots (273,285,553,554 and 555) and headache that is exacerbated by stooping or Valsalva suggests raised intracranial pressure (556).

Nonvolitional. Coughing and sneezing are nonvolitional movements that generate a Valsalva maneuver (329). Valsalva maneuvers can precipitate transient elevations in intracranial pressure called “plateau waves.” In patients with cerebral tumors, these plateau waves can be associated with short periods of severe headache, nausea, vomiting, photophobia, lethargy, and transient neurological deficits (331,332). Occasionally these plateau waves produce life-threatening herniation syndromes (331,332). Similarly, among patients with spinal cord compression, the transient pressure shifts can exacerbate back or radicular pain.

Neuropathic, Nonmovement-Related Breakthrough Pain

Transient episodes of spontaneous lancinating or burning pain are a common manifestation of neuropathic pain syndromes. The frequency of pain exacerbations is very variable; from many hundred episodes of brief lancinations per day, to vary rare episodes with weeks to months between events (550). Lancinating neuropathic pains are often of very brief duration. This feature has therapeutic implications insofar as responsive analgesia is not likely to take effect until well after the pain has resolved and is thus not likely to be effective. This sort of pain commonly requires a preventative therapy to diminish the frequency and severity of events (42,49,557,558).

Visceral Breakthrough Pains

Visceral nociceptors respond primarily to mechanical and chemical nociceptive stimuli. Functionally, there is evidence for three classes of visceral afferents: low-threshold mechanosensitive afferents which respond to distention and contraction, specific chemosensitive afferents, and high-threshold mechanosensitive afferents (559).

Volitional. Initiation of the activity of some visceral organs is influenced by volitional activity. This is true for upper, gastrointestinal-tract activity associated with swallowing and digestion, micturition, defecation, and sexual climax (male and female). Indeed exacerbations of visceral pain may be associated with any one of these activities. Transient visceral pains initiated by volitional activity may benefit from preemptive therapies or specific therapies targeted at the underlying mechanism.

Nonvolitional. Visceral motility is usually spontaneous and is often unrelated to any volitional activity. Spontaneous muscular contractions of hollow organs commonly results in paroxysmal transient pain exacerbations. Pain of this sort is commonly generated by the esophagus, intestines, gallbladder, and urinary bladder. Obstruction or inflammation of any hollow viscus may generate paroxysmal pains associated with spontaneous muscle contraction.

CONCLUSION

Adequate assessment is a necessary precondition for effective pain management. In the cancer population, assessment must recognize the dynamic relationship between the symptom, the illness, and larger concerns related to quality of life. Syndrome identification and inferences about pain pathophysiology are useful elements that may simplify this complex undertaking.

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2

BONE PAIN: ASSESSMENT AND MANAGEMENT

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Approximately 60–84% of cancer patients with solid tumors develop bone metastases (1). Although almost any tumor can spread to bone, some are more osteotropic than others. Breast and prostate cancer, along with multiple myeloma, lung, thyroid, and kidney tumors, metastasize to bone more frequently. Nielsen et al. (2) demonstrated at autopsy that up to 85% of patients with breast, lung, or prostate cancer have bone involvement. The metastatic spread to bone is primarily due to the hematogenous spread of tumor cells from a primary tumor. After a tumor grows through the wall of a blood vessel, tumor cells are released and can be distributed to other organs or bone. Substances released during normal bone resorption may act as chemotactic factors in cancer patients and disrupt the normal bone remodeling process. Parathyroid hormone-related protein and cytokines induce this disruption by the induction of osteoclasts, usually resulting in a net loss of bone at the site of increased activity. Osteoblastic activity may not equal osteoclastic activity, or the site may not be able to attract osteoblasts. Lytic bone lesions result from this net loss of bone and are a significant cause of morbidity in cancer patients with bone metastases. Complications include pain, pathological fracture, loss of functioning and mobility, inadequate hematopoiesis due to bone marrow involvement, disruption of calcium homeostasis with the development of hypercalcemia, and spinal cord compression. Bone pain is the most frequent cause of morbidity. Furthermore, the most common pain syndrome encountered in cancer patients is that of metastatic bone pain (3).

PATHOPHYSIOLOGY OF BONE PAIN IN CANCER

Several mechanisms are probably involved in the pathophysiology of bone pain. The two most likely mechanisms that contribute to pain in bone metastasis include the inflammatory mediators, such as prostaglandins (PGs), and mechanical stimulation of nociceptors when the tumor mass distorts the periosteum and increases intraosseal pressure. Bone metastases are associated with edema and inflammation so that nociceptors are activated and sensitized by chemical mediators of the inflammatory response such as PGs, bradykinin, and potassium (4).

PG biosynthesis appears to be involved in the process of bone destruction and in the new bone formation that accompanies bone metastases. PGs in the A and E series may stimulate tumor cells directly, whereas PGs in the E series are involved in osteoclastic bone resorption and enhance interleukin-1 (IL-1), which is involved in bone metastasis. In addition to PGs, other humoral mechanisms involved in osteolytic destruction of bone in bone metastasis include cytokines, growth factors, and parathormone (5). Many of the chemical mediators such as IL-1, IL-6, and tumor necrosis factor involved in osteolysis also activate nociceptors (6).

The gender or age of the patient, the type of tumor, and the location, number, and size of metastases do not correlate well with the presence or absence of pain (7). Patients with multiple bone metastases usually report pain only at a few sites, and more than 25% of patients with bone metastases are pain-free (8). It is probable that pain receptors are activated by cytokines and other algesic chemicals in the bone marrow. Other causes of pain secondary to bone metastases include reactive muscle spasm, nerve root infiltration, and nerve compression.

CLINICAL PRESENTATION

The most common presentation of osteolytic bone metastases is pain. The pain is usually somatic and is characterized by a dull ache that is well localized and is increased with weight-bearing or at night. The pain is usually constant, gradually increasing in intensity, and is exacerbated by different positions or movements.

The sites most commonly involved in bone metastases include the pelvis, vertebrae, femur, ribs, and skull (9). Metastases to these areas often lead to pain that occurs during changes in posture or body position. Such pain is called *incident* pain and is difficult to manage with analgesic therapies alone. When a patient experiences incident pain, the best treatment often consists of removal of the tumor, with or without orthopedic stabilization or denervation of the painful part, such as with neurolytic anesthetic techniques or cordotomy. Many different symptoms and syndromes are associated with pain from bone metastases. Bone pain can be referred, and a secondary pain can be caused by reactive muscle spasm (10). Bony lesions that infiltrate and compress nerves may cause paroxysms of sharp, shooting, lancinating pain. Several different specific syndromes are associated with neurological involvement, including vertebral syndromes and metastases to the skull (11).

The most common site of bone metastases is the vertebrae, with more than two-thirds of cases affecting the thoracic spine, 20% affecting the lumbosacral spine, and 10% affecting the cervical spine (12). More than 85% of patients have metastatic bone involvement at multiple levels (13). Early recognition of pain due to tumor involvement is essential because pain usually precedes tumor compression of adjacent neural structures, which can result in the development of irreversible neurological deficits.

Four well-recognized vertebral syndromes secondary to bone metastases include atlantoaxial destruction and odontoid fracture, C7-T1 syndrome, T12-L1 syndrome, and sacral syndrome (Table 2-1). Atlantoaxial destruction and odontoid fracture usually present with nuchal or occipital pain radiating from the posterior aspect of the skull to the vertex. Usually this pain is exacerbated by flexion of the neck. Concomitant compression of the spinal cord at the cervicomedullary junction is accompanied by sensory, motor, and autonomic involvement of the upper extremities. Magnetic resonance imaging (MRI) is probably the best method for visualizing this area of the spine.

Syndrome	Presentation of pain
Atlantoaxial destruction and odontoid fracture	Nuchal or occipital pain radiating from the posterior aspect of the skull to the vertex.
C7-T1 syndrome	Pain exacerbated by flexion of the neck. Pain referred to the interscapular region.
T12-L1 syndrome	Pain referred to sacroiliac joint or ipsilateral iliac crest.
Sacral syndrome	Pain radiating to buttocks, perineum, and posterior thighs, exacerbated by sitting or lying down. Relieved with walking or standing.
"Pyriformis syndrome"	Buttock or posterior leg pain with internal rotation of the hip if the neoplasm spreads laterally to involve muscles that rotate the hip.

TABLE 2-1. VERTEBRAL PAIN SYNDROMES

The C7-T1 syndrome involves pain that is referred to the interscapular region. In assessing for this syndrome, it is essential to have patients undergo radiography of both the cervical and the thoracic spine. Pain from a T12 or L1 lesion is usually referred to the sacroiliac joint or the ipsilateral iliac crest. Destruction of the sacrum may cause severe pain that radiates to the buttocks, perineum, or posterior thighs. This pain is relieved with walking or standing and is exacerbated by sitting or lying down. If the tumor metastasizes to muscles, such as the pyriformis, the patient will experience severe incident pain of the buttock or posterior leg with internal rotation of the hip. The tumor can also infiltrate nerves, which leads to a sacral plexopathy (14).

In evaluating a patient with back pain, it is important to keep in mind that almost all patients with epidural compression initially present with back pain and that it occurs in 10% of patients with cancer. Epidural compression is the second most common neurological complication of cancer (15). Some characteristics of back pain are clearly suggestive of epidural extension. These include back pain that rapidly progresses in intensity, and radicular pain that is either lancinating or constant. When the back or radicular pain is exacerbated by coughing, sneezing, straining, or recumbency, the likelihood of epidural compression is greater. In the thorax, the radicular pain may present as a belt-like band across the abdomen or chest, whereas in the lumbosacral or cervical regions the radicular pain is usually unilateral. Because back pain precedes neurological signs, it is essential to undertake a diagnostic evaluation at a time when the neurological evaluation is still normal.

Other sites of metastatic involvement include the bony pelvis and hip. Tumor involvement of the acetabulum or head of the femur usually produces localized hip pain, which is aggravated by weight-bearing or ambulation. The pain may radiate to the medial thigh or knee and is usually an incident pain with ambulation. Evaluation by computed tomography (CT) or MRI is essential to demonstrate the extent of bony destruction. Bone pain can be focal, multifocal, or generalized. Multifocal bone pain is usually secondary to bone metastases in multiple areas. However, rarely there is generalized bone pain caused by replacement of bone marrow. This bone marrow replacement syndrome is more common in hematogenous malignancies than solid tumors (16). This syndrome may be difficult to diagnose because it can occur in the absence of any abnormalities on bone scintigraphy or radiography. Moreover, another rare syndrome, paraneoplastic osteomalacia, can mimic multiple metastases. Other possible nonneoplastic causes of bone pain that must be differentiated from bone metastases include osteoporotic fractures and focal osteonecrosis, which may be related to corticosteroids or radiotherapy.

ASSESSMENT OF BONE PAIN

Development of individualized treatment for the patient with osseous metastases requires diagnostic imaging. Although now in use for more than 100 years, plain x-ray imaging continues to be important in the definition of bony changes secondary to neoplastic disease. It is particularly important in the assessment of cortical integrity of long bones (17) and almost invariably demonstrates abnormality in areas of epidural compression (18). Although it lacks the sensitivity of bone scanning, it complements it and is still useful in diseases that are predominantly osteolytic, especially multiple myeloma.

Radionucleotide bone scanning is probably the most widely used radiographical procedure for detection of suspected metastatic disease. Because of its ability to detect asymptomatic disease, it is favored in the initial staging of many carcinomas. Conventional technetium-99m (Tc-99m) bone scanning, which reflects osteoblastic activity, is an order of magnitude more sensitive than plain x-rays (19). It is a very important extension of the physical examination, it can aid in evaluation of the results of therapy and, above all, it provides superior anatomical characterization when a target for external beam radiation is being selected. In the emerging field of bone-seeking radioisotopes, bone scanning may also serve to measure the administered dose to bone metastases (20).

Although not suitable for screening asymptomatic patients for occult disease, MRI is even more sensitive than bone scanning for marrow lesions (21) and is therefore useful when the bone scan fails to reveal spinal lesions in the symptomatic patient. It is extremely useful in differentiation of soft tissue from bone in spinal lesions and in depiction of the soft-tissue component of bone disease when that knowledge is necessary for treatment planning.

CT, although now largely supplanted by MRI in the evaluation of spinal disease, continues to be appropriate in a more limited set of circumstances. CT retains a role in patients with suspected spinal epidural disease when the level is known with certainty and the MRI cannot be performed. In addition, CT remains important in the evaluation of pelvic and thoracic wall disease.

TREATMENT OF BONE PAIN IN THE CANCER PATIENT

The treatment of pain caused by bone metastases involves the use of many different approaches based on the needs of the individual patient (Table 2-2). The complementary approaches employed include non-opioid and opioid analgesics, bisphosphonates, antineoplastic therapies and, less commonly, neurosurgical and anesthetic procedures. To improve mobility, the treatment plan should also include physiotherapy and occupational therapy.

Surgery
Radiation therapy
External beam radiation therapy
Local field radiotherapy
Wide-field radiotherapy
Systemic radionuclides
Strontium
Sm-153 EDTMP
Chemotherapy
Hormonal therapy
Hypophysectomy
Nonsteroidals
Opioid analgesics
Corticosteroids
Calcitonin and gallium nitrate
Bisphosphonates
Neural blockade
Spinal analgesia
Cordotomy or pituitary ablation
Physiatry, physical therapy

TABLE 2-2. DIFFERENT MODALITIES FOR THE TREATMENT OF BONE PAIN SECONDARY TO BONE METASTASES

RADIOTHERAPY

Despite great progress in pharmacological pain management, hormonal manipulations of breast and prostate cancer, prevention of metastases with osteoclast inhibitors, cytotoxic chemotherapy, and other approaches, radiation remains important and perhaps underutilized in the treatment of osseous metastases (22).

There is potentially an expanded role for radiotherapy in the treatment of bone metastases, and there is a need for better definition of its indications and applications. The traditional prescription of 3 Gy administered on ten occasions to all sites of bone pain, regardless of diagnosis, performance status, or the results of staging, is antediluvian in the light of advances in diagnostic imaging and surgical techniques, newer forms of radiation therapy, and the increasing (although still far from adequate) knowledge of prognosis based on modern statistical investigations. The above considerations suggest the need for an individualized approach to radiotherapy prescription.

RADIOBIOLOGY OF BONE AND BONE MARROW

Discriminating among treatment strategies requires insight into the effects of radiation on bone and bone marrow. When photons strike bone and tumor, a stereotypical cascade of events occurs, culminating ideally in elimination of the cancer and restoration of normal healing of bone. However, achieving this necessitates skillful manipulation of time, dose, and fractionation. For an exhaustive discussion of these topics, the reader is referred to Rubin and Casarett's textbook of radiation pathology (23) and to Hall's textbook of radiobiology (24). However, a few concepts are necessary before we continue discussion of the radiotherapy of bone metastases.

There are several consequences to radiation of the bone marrow. First, there is an immediate and complete intermitotic elimination of the megakaryocytes and of red cell and leukocyte precursors within the irradiated bone marrow, along with an analogous necrosis of circulating lymphocytes, which are similarly sensitive. Mature red cells are unaffected. The net effect, if the field is large enough, is a rapid depopulation of circulating lymphocytes with more general leukopenia and thrombocytopenia following in a few days. In general, leukopenia and thrombocytopenia peak at 3 weeks after exposure and recover over 4–6 weeks. Anemia, if it occurs, does not usually appear for several months, consistent with the long circulating life of mature red cells. Rapid proliferation of the remaining bone marrow determines hematopoietic recovery but not repopulation of the irradiated area, which may take a year or more. Therefore, in patients with generally compromised bone marrow, whether caused by disease, by chemotherapy, or by previous radiation, recovery may be incomplete or delayed for long periods even at doses below that expected to

cause irreversible stromal damage (a late effect). Delayed bone marrow recovery occurs only at cumulative doses greater than 40–50 Gy delivered by conventional fractionation schedules, and the reaction is characterized not by the typical radiation fibrosis, but by replacement of the hematopoietic tissues with adipocytes, precluding any recovery of the irradiated area.

Fortunately, bone is more radioresistant than bone marrow. However, radiation may nevertheless have undesirable consequences. Radiation at doses characteristically employed in the treatment of metastases can be expected to temporarily inhibit chondrogenesis (25), which may delay healing in irradiated areas. Patients should therefore be informed that weakened bone needs time to repair itself. From the patient standpoint, radiation cannot be expected to result in rapid and complete relief of symptoms, and weight-bearing bones that are compromised may fracture before successful remodeling and repair are completed. In addition, doses in excess of 50 Gy extensively damage small vessels and may result in avascular necrosis of bone.

CRITERIA FOR SURGERY

Although radiation is the mainstay of treatment for bone metastases, adjuvant surgery should be considered in two instances: epidural compression and extensive lytic involvement of weight-bearing bones. Unfortunately, in neither instance are interventional criteria well established, and good practice necessitates clinical judgment.

In the case of extensive lytic involvement of long bones, literature can be found both favoring early and vigorous operative intervention (26) or questioning its merit (27). Pathological fractures involve the proximal femur more than other sites (28) and, for obvious reasons, the consequences are graver than those of fractures at other sites; this is the case in which internal fixation is most often considered. The American College of Radiology (ACR) consensus panel on radiation of bone metastases (29) recommends surgical stabilization for lytic lesions greater than 3 cm and involvement of greater than one-third of the cortex.

Determining whether or not surgery should be used to relieve epidural compression caused by vertebral metastases is often difficult. Normally, radiation therapy is the first choice for treatment of these lesions because the additional use of surgery has not demonstrated to improve outcome (12,30,31), and most patients who are ambulatory at the time of diagnosis will remain ambulatory after radiation alone. In one analysis, the proportion of patients ambulatory after radiation therapy was 96% if they walked in at diagnosis (32).

Settings deemed appropriate for surgery include diagnostic uncertainty, unstable vertebral relationships, radiation failure, large paravertebral masses, and perhaps the rapid progression of neurological symptoms (30). It is noteworthy that the ACR consensus committee (32) reached agreement on only one of three clinical vignettes concerning the use of operative intervention and spinal metastases. In the proffered vignette, a patient with symptomatic epidural compression in a previously irradiated area, the group felt that posterior decompression was appropriate.

PROGNOSIS

Once a patient develops bony metastases from carcinomas, the disease is considered incurable. However, the duration of survival and the quality of life may vary tremendously. In the three most common malignancies—breast, lung, and prostate—breast metastases have the best prognosis and lung the worst. In patients with breast cancer and metastases limited to bone, median survival is approximately 3 years (33). Prostate cancer patients with a high performance status, lower alkaline phosphatase levels, and higher hemoglobin may live many years (34,35). In an interesting examination of patients with unknown primaries (36), a group from the Rotterdam Cancer Institute found that in a multivariate analysis only performance status and alkaline phosphatase were predictive of outcome, with those patients whose alkaline phosphatase was less than 1.25 times normal and with the World Health Organization performance of 0 having a median survival of greater than 4 years. Unfortunately, no literature comprehensively addresses this topic, and there is a compelling need for more information related not only to prediction of life expectancy but also to quality of life.

EXTERNAL BEAM RADIOTHERAPY

Conventional Field Sizes

The ideal radiotherapy prescription for the palliation of pain from bone metastases differs markedly from that prescribed for curative treatments. In the case of the latter, there is less concern about overall treatment time and acute side effects, the goal being to maximize cure rates at a reasonable level of risk. In contrast, palliative treatments are intended to maximize the chances of local control during the patient's limited life span while minimizing the inconvenience and acute side effects associated with a protracted course of fractionated radiotherapy. Often palliative radiotherapy courses are administered using hypofractionation, which would be unacceptable in the patient treated definitively because of the serious risk for long-term complications and the often low rates of longterm control. Nevertheless, care must be taken in patients with a greater than 1-year life expectancy not to expose them to undue risk for pathological fracture because of high-dose/large fraction size or spinal cord compression from an inadequately treated region.

The current literature deals extensively with the central issues of dose and fractionation in teletherapy of bone metastases. Tong et al. (37) and the subsequent reanalysis by Blitzer (38) are the landmark publications in the investigation of how to treat bony metastases with external beam radiation. These articles report and analyze the Radiation Therapy Oncology Group (RTOG) 74-02 study, which is the largest randomized trial looking specifically at time, dose, and fractionation, with a total of 1016 randomized patients.

Earlier case series and nonrandomized investigations had suggested a wide range of possible treatment schedules for bone involvement. Jensen and Roesdahl (39) found good relief in 85% of patients treated with 3–7 Gy. Allen et al. (40) found effective palliation at NSD doses ranging from 500 to 1700 in various fractionation schemes. Penn found that at 6 months 70% of patients had achieved complete or almost complete palliation with either 3 Gy administered 10 fractions or with single fractions from 8–15 Gy. In the study of Hendrickson et al. (41), patients who received an NSD of 900 achieved the same degree of analgesia as patients receiving one of 1200 (equivalent to 5% 4 Gy or 10% 3 Gy in daily fractions). Gilbert et al. (42) found that 63% of patients who survived more than 3 months had a satisfactory quality of life after radiation and that radiation dose did not correlate with quality of life. Somewhat surprisingly, Garmatis and Chu (43) found that recalcification occurred in 75% of patients irradiated to a total dose of only 20–25 Gy in 2.0- to 2.5-Gy fractions.

RTOG 74-0237 divided patients into two groups: those with solitary metastases and those with multiple bone metastases. Those with solitary metastases were randomized to receive either 40 Gy in 3 weeks or 20 Gy in 1 week. Those with multiple osseous lesions received either 30 Gy in 2 weeks, 15 Gy in 1 week, 20 Gy in 1 week, or 25 Gy in 1 week. Patients scored their own pain severity and frequency and the frequency of pain medication administration. Overall, 83% achieved partial or complete pain relief. Some 86% of the patients experienced some pain relief in the first 2 weeks, and almost all patients by the end of 4 weeks. Complete relief was slower, coming more than 4 weeks after the commencement of treatment and consistent with the healing of injured bone. The rapidity of pain relief was somewhat less in those with pelvic metastases and those treated with the 3-week fractionation scheme. Patients with prostate and breast cancer tended to fare better than those with lung cancer.

In the initial analysis (37), inferential statistics were performed on the two sets of patients—the solitary metastases group and the group with multiple metastases—individually, reducing the power of the study. No statistically significant differences emerged between groups with reference to pain control, although there appeared to be a trend toward better control in the higher-dose sets (30 and 40.5 Gy). Blitzer in his reanalysis (38), however, approached the analysis from a different perspective. He reasoned that both the cohort with solitary metastases and those with multiple metastases could be expected to achieve local relief similarly and that there was therefore no reason to perform separate inferential analyses. In addition, he controlled for the effect of retreatment on long-term pain control. Blitzer found a rather striking stepwise association between the combined effect of higher doses and greater numbers of fractions and complete pain relief, but did not find that a dose response was quantifiable using classical time-dose factor conversions.

More recent randomized trials have demonstrated that fractionation schemes ranging from 8 Gy × 1 to 4 Gy × 5 are equally effective in producing palliation for most patients (44,45 and 46). A study from the Royal Marsden Hospital did, however, conclude that a single dose of 4 Gy was insufficient to maintain durable control (47).

The preponderance of evidence about external beam radiation favors short, even single-fraction irradiation for most palliative situations, with the caveat that retreatment may be both necessary and feasible in the lowest dose/fractionation schema. The ACR Consensus Committee suggested a wide range of acceptable prescriptions, 5% 4 Gy to 14% 2.5 Gy, but did suggest caution in generalizing these to all presentations (31). They pointed out that 6 × 6 Gy might be an appropriate fractionation schedule for melanoma, a tumor known to be radioresistant because of the efficient repair of sublethal damage, and 15% 2.5 Gy was considered appropriate for hypernephroma metastases because of possible radioresistance. Single-fraction schedules are probably not appropriate if large amounts of bowel are in the field, because the consequent diarrhea or nausea is not justifiable in a patient with limited life expectancy.

Wide-Field Radiotherapy

Although large fields and total body irradiation have been used for the greater part of this century in lymphoid malignancies, the modern era of wide-field radiotherapy

for the relief of osseous metastases began in the early 1970s. Investigators (48) from Princess Margaret Hospital, discouraged by the frequency of retreatment, developed the concept of half-body radiation. This technique required the sequential treatment of the two halves of the body. They postulated that 8 Gy would produce 99.5% cell kill, enough for a remission but clearly far beyond the tolerance of stem cells within the bone marrow (4–5 Gy). They hypothesized that the unirradiated bone marrow would rapidly repopulate the stem cells killed in the initial hemibody exposure and that this would permit treatment of the other half of the body 4–6 weeks later. The treatment was administered in less than 1 hour and the eyes and upper skull were shielded. These investigators noted the occurrence of the acute radiation syndrome of total body irradiation (vomiting and diarrhea, and occasionally fever, occurring for a few hours after exposure) in the majority of patients irradiated to the upper half of the body, but little in the way of acute toxicity following treatment of the lower half of the body. Salazar et al. (49) noted that the limiting factor was pulmonary toxicity, which occurred in 9% of patients treated at 8 Gy.

Because of the many issues of dose and toxicity involved in wide-field radiotherapy, the RTOG began a trial in 1978 looking at hemibody radiation for bone metastases. The final report of RTOG 78-1050 provided extensive guidelines for the use of this technique. These patients were treated to the upper, mid-, or lower body with simple parallel opposed fields delivering about 30 cGy per minute. Upper body patients were hospitalized and premedicated to lessen the severity of the acute radiation syndrome. The final analysis revealed that single-dose hemibody radiation provided complete pain relief in about 20% of the patients and some pain relief in about twothirds. The treatment was felt to be endurable by about 50% of the patients. Median time to pain relief was 1–2 days, in contrast to the patients in RTOG 74-02, who generally achieved pain relief only after several weeks. However, almost twice as many patients were able to obtain complete relief with more conventionally fractionated radiation delivered to local fields. Only mild pneumonitis was seen, and approximately 11% of the patients experienced life-threatening hematological toxicity. The investigators felt that the safest and most effective doses were 6 Gy for upper body and 8 Gy for lower and mid-body treatments.

RTOG 82-0651 examined whether the addition of hemibody irradiation to local field radiation retarded disease progression. Modest improvement was seen in disease progression at 1 year (35% vs. 46%) and a more impressive difference in the time to disease progression in the irradiated hemibody (12.6 vs. 6.3 months). The issue of fractionated wide-field radiotherapy was also examined by the RTOG. A small trial (52) suggested an improvement in the median duration of palliation, but RTOG 88-22 (53), which looked at the addition of several schemes of fractionated wide-field radiation to the local administration of 3 Gy and did not conclude that there was any advantage over single-dose administration.

Wide-field radiotherapy has the advantage of providing more rapid pain relief. It also increases the time to retreatment at other metastatic sites and may improve local control when added to localized irradiation. Hemibody radiation is more toxic than conventional treatment. The most daunting problems are management of the acute radiation syndrome in upper body patients and hematological suppression, which may be life threatening.

SYSTEMIC RADIONUCLIDES

Radiopharmaceutical agents are an attractive alternative to wide-field radiotherapy. Because they do not evoke the acute radiation syndrome and can be administered over a few minutes, their use is less cumbersome. The field of artificial radioactivity, developed by the Joliot-Curies in the 1930s, has provided a host of isotopes not found in nature, some of which are useful for treatment. Perhaps the best known is iodine-131 (I-131), useful in the palliation and treatment of thyroid carcinomas but is not generally applicable for palliation of bone metastases and is therefore beyond the scope of this discussion. However, in the past decade, interest in the palliative use of radioisotopes has been rekindled, largely because of the U.S. Food and Drug Administration approval of strontium chloride-89 (Sr-89) several years ago.

Prior to 1990, phosphorus-32 (P-32) was used occasionally for pain relief in bony metastatic disease. P-32, which has a half-life of 14.2 days and an average energy b-particle of approximately 695 keV, is cumbersome to use because of the ubiquitousness of P-32 in intracellular metabolism. As a result, doses required to obtain a tumor response in bony metastatic disease prove excessive for bone marrow tolerance. Because of the pronounced myelosuppression and thrombocytopenia, the use of P-32 has largely been abandoned for this indication.

Sr-89 has a number of advantages over P-32. It mimics the metabolism of calcium and consequently is found where bone turnover is greatest (54). Because bone metastases produce a luxuriant osteoblastic response, the accumulation of Sr-89 is severalfold greater in areas of metastatic disease than in normal bone. In addition, the Sr-89 is washed out of the normal bone but is fixed in a stable configuration within the area of metastatic bone disease (55). Sr-89, a b-emitting isotope with a physical half-life of 50.5 days, has a mean energy of approximately 1.5 MeV. It does not emit a b-particle. The biological half-life of Sr is about 14 days in normal bone and is virtually the same as the physical half-life in metastases. This is an obvious therapeutic gain over P-32 and results in doses to metastases estimated to be 8.5 Gy per mCi (56).

Strontium-89 in solution is administered intravenously over 2 minutes. To be eligible for treatment, Nycomed/ Amersham, the manufacturer, suggests that patients have adequate white blood cell and platelet counts. There is appreciable excretion in the urine over a 1-week period, and this can present a problem in patients with bladder dysfunction. It is virtually free of acute side effects. About 10% of patients develop a “flare” reaction with increase in pain, which is of no particular prognostic significance. Sr-89 is generally easy to manage with steroids and nonsteroidal anti-inflammatory drugs (NSAIDs). The major toxicity is myelosuppression. In general, this becomes apparent in 3–4 weeks and recovers to some degree at the end of 3 months, the earliest time at which the manufacturer suggests repeat administration.

The current recommended dose is 4 mCi. However, the issue of dose is not well established. In the United Kingdom Metastron (57) trial, 5.4 mCi of Sr-89 was used and was compared to local radiation and hemibody radiation. The results suggested that patients on this study did as well with Sr-89 as with hemibody radiation and better than with local radiation only. The Trans-Canada trial (58) showed Sr-89 to be an effective addition to local field radiation. A total of 126 patients received local field radiotherapy and either 10.8 mCi of Sr or placebo. This study focused very specifically on quality of life issues and demonstrated a markedly decreased analgesic intake with Sr-89, as well as a significant number of complete responses. Although objective antitumor responses are relatively transient with Sr, there was a statistically significant difference in decrease in prostate-specific antigen between the group that received Sr in the Trans-Canada trial and patients who received placebo. Pain relief typically began 10–20 days after injection. In a recent study from the Health Economics Unit at Gothenburg (59), the analysis suggested that the addition of Sr-89 to local radiotherapy would be more cost-effective than no further treatment; the potential cost savings derived from the reduction in radiotherapy retreatments.

Recently, a number of chelating agents have been used to bind metals and form bone-seeking ligand complexes that are stable and chemically active in osteoblastic metastases. As of this writing, the only one that has full Food and Drug Administration approval is samarium 153-EDTMP, which is avidly bound by osteoblastic metastases and excreted intact in the urine within 12 hours (60). Sm-153 has some potential advantages over Sr-89: a shorter half-life (46 hours) and a gamma-emission useful for imaging (103 keV) while retaining betaradiation with a range of 1.7 mm. As a result, pain relief can be expected to be more rapid and the myelotoxicity of lesser duration than seen with Sr-89. Clinical studies have tended to support these anticipated outcomes (60,61), showing pain relief within a week or two and hematological recovery within 2 months. In two recent controlled trials (61,62), pain palliation was observed in roughly 70% of patients, which was comparable to that seen in the Sr-89 trials, and a benchmark dose of 1.0 mCi per patient was established.

A number of radioisotope ligand complexes are candidates for use in treatment of bone metastases. These include Re-186, Re 188-HEDP, and Sn117m DTPA (63,64,65,66,67,68,69,70,71 and 72,74). Of these, the most clinical data are available on Re-186. This isotope, which has a half-life of 3.77 days and an average beta-energy of 323 keV, has a gamma-ray yield of 8.5%. The gamma has an energy of 137 keV, again very suitable for imaging. A single i.v. infusion of 30–35 mCi of Re-186 has been associated with significant pain relief in 80% of patients. (68) In an interesting study design, Re-186 was evaluated with a double-blind crossover comparison to Tc 99-MDP as placebo (69). There was a significantly reduced pain requirement. Toxicity was primarily hematological, although the authors found it difficult to distinguish in the crossover design between the results of treatment and those of the disease itself with respect to the white count. The platelet count appeared to be depressed from baseline to between 60,000 and 90,000. The authors noted that all blood counts had returned to baseline by the end of the 8-week study and that this was double the recovery reported for strontium chloride. More recent studies have confirmed thrombocytopenia as being the dose-limiting factor for this isotope (64,65 and 66,71), and in one study (64) of prostate cancer patients the pretherapy Tc bone scan correlated highly (r2 = 0.78) with the degree of platelet decline.

Radioisotopes provide an alternative option to widefield radiotherapy. They are easier to administer and have less acute toxicity. Although the promptness of pain relief is less, the available literature suggests that pain relief is still relatively rapid, within 1–2 weeks, and that the ultimate degree and duration of pain relief compare very favorably with those achieved by hemibody irradiation.

SUMMARY OF RADIOTHERAPY

Despite the excellent advances in pharmacological intervention over the past few decades, radiotherapy remains firmly entrenched as an important form of palliation for metastatic disease. To maximize its utility, individualized treatment strategies should be developed. These require, foremost, a subjective judgment of the patient's prognosis. In addition, diagnostic imaging should be used appropriately as necessary and the clinician should be aware of the indications for surgery in patients with metastatic disease to the spine and long bones.

Most of the literature favors the use of shorter fractionation schemes. The convenience of hypofractionation and the possibility of retreatment appear to negate any dose-response advantage to greater numbers of fractions and higher doses. Wide-field radiotherapy can improve on the results of local field radiation and has the advantage of providing more rapid relief of pain. However, it is technically daunting, and upper body radiation is associated with the acute radiation syndrome and the

necessity for hospitalization. As a result, bone-seeking radionuclides are becoming more enticing and the field is burgeoning with the development of new isotopes (72). These isotopes have many advantages over wide-field radiotherapy and are lacking only in some of the promptness of relief that one observes with wide-field radiotherapy.

Despite all the conclusions of the recent literature, the medical establishment has been dilatory in implementing new radiotherapeutic approaches to relieve bone pain. Although there are substantial variations in palliative practice among different countries, there is a general tendency to resist the most efficient strategies (72a,72b and 72c). Some of this variability can be attributed to different health care systems and different economic incentives. The Canadian standard palliative regimen for bone metastasis is five fractions instead of the typical ten-fraction regimen in the United States, and they do employ radionuclides and wide-field radiotherapy more readily (72a), but there is still resistance to the use of single fractions that can be attributed purely to monetary influence and may simply be related to tradition and inertia (72b,72c). Why the overwhelming evidence from clinical trials has influenced practice so modestly is curious and worthy of further inquiry.

CHEMOTHERAPY

The degree of palliation of pain from bone metastases is difficult to measure with the use of chemotherapy. It would be expected that, if there is an objective response rate, chemotherapy would also benefit pain relief. However, this is not always the case; patients sometimes experience pain relief without any objective tumor response (73). In some tumors for which chemotherapy is effective, a small percentage of patients with bone metastases may report pain relief with it. These tumors include breast cancer, smallcell lung cancer, lymphoma, multiple myeloma, and germcell tumors (74). Pain responses that may occur with chemotherapy can begin 2 weeks after the chemotherapy is received (75). There is very little justification for the use of chemotherapy for bone pain in patients with cancer that is very far advanced. The toxicity of the chemotherapy in patients with far-advanced disease far outweighs the benefits.

HORMONAL THERAPIES AND HYPOPHYSECTOMY

Endocrine therapy hormone-dependent tumors, such as metastatic breast, prostate, or endometrial carcinoma, may be effective at relieving bone pain while treating the tumor. Endocrine manipulation may produce pain relief in 50% of patients with hormone-responsive breast tumors (76). Patients with prostate carcinoma treated with gonadotrophin agonists or other hormones may experience sustained pain relief, even with widespread bone metastases (77).

Chemical hypophysectomy has been used in the past and may provide pain relief in as many as 35–93% of patients (78). To obtain pain relief does not require complete hypopituitarism or even a hormone-responsive tumor. The pain relief obtained usually lasts up to 20 weeks. However, chemical hypophysectomy is usually reserved until after radiation therapy has failed, and is currently rarely performed.

The role of levodopa, which is an inhibitor of prolactin release, is unclear in the management of painful metastatic lesions in the bone. An early study (79) in the 1970s noted that 33% of patients with breast carcinoma metastatic to bone reported pain relief when given levodopa. A suggestion made at that time was that responsiveness to levodopa might predict responsiveness to hypophysectomy. However, a more recent study revealed that only one of 14 patients with metastatic bone pain experienced any pain relief with carbidopa-levodopa (80). Therefore, additional studies are required to define the role of levodopa in relief of bone pain.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The mainstay of drug therapy for cancer pain relief includes the NSAIDs and opioids. NSAIDs are believed to be effective in the treatment of bone pain by virtue of their actions on PG synthesis. A decrease in PGs leads to a reduction in PG-induced pain sensitization and also reduces edema which, if present, can increase intraosseous pressure and stretching of the periosteum. Another action of NSAIDs, independent of a decrease in PG synthesis, is a direct effect on spinal nociceptive processing (81). It is probable that both of these mechanisms are involved with the use of NSAIDs in bone pain because it is now understood that skeletal pain involves both peripheral and central mechanisms (1).

It is important to understand that NSAIDs, unlike opioids, have a “ceiling” to their analgesic effect. The minimal analgesic dose for the individual patient with pain secondary to cancer is unknown. However, failure with one NSAID may be followed by success with another NSAID. Therefore, if a patient is not having moderate or severe pain one can attempt sequential NSAID trials (82). With more severe pain, an opioid should be started immediately. Maximal doses for nonsteroidals generally recommended for analgesia are no more than 1.5–2.0 times the standard recommended dose. It is difficult to ascertain the value of NSAIDs in bone pain because bone pain per se was usually not separated from cancer pain of other origins in the controlled clinical trials done with NSAIDs. Patients with cancer who are receiving many medications may benefit from a long-acting NSAID once or twice a day. However, there is also some suggestion that a shorter-acting NSAID may be useful in the treatment of incident bone pain (1).

Several placebo-controlled, prospective studies have shown NSAIDs to be efficacious in the treatment of cancer pain. In a placebo-controlled study that compared ketoprofen, 100 mg and 300 mg, versus aspirin and codeine, ketoprofen, 100 mg, provided pain relief superior to that achieved in the other two arms of the study. The side effects in all three arms were approximately the same (83). In another study that compared i.m. morphine, 5 mg and 10 mg, versus p.o. ketoprofen, 75 mg and 200 mg, in patients with cancer pain, including bone pain, within the first hour patients obtained more pain relief from the morphine. However, 2–3 hours after administration patients reported more pain relief from both doses of ketoprofen (84).

Several studies have suggested that combination analgesia is superior to either NSAIDs or opioids alone. One study compared the combination of ibuprofen, 600 mg, and methadone, 2.5 mg and 5.0 mg, and found that the combination of the NSAID with the opioid provided better pain relief than methadone alone for cancer pain (85). In another study in patients with moderate-to-severe cancer pain, adequate analgesia was obtained with the use of oxycodone. After this, either a placebo or ibuprofen was added to the analgesic regimen. This study found a significant reduction in the amount of oxycodone needed to manage the pain in the patients who received ibuprofen compared to those who received placebo (86).

The most significant factor limiting the use of NSAIDs is their toxicity profile. NSAIDs are associated with potentially serious side effects, which can include gastrointestinal bleeding, suppression of fever with a resultant undetected infection, and renal toxicity, particularly in patients receiving concomitant chemotherapy. The nonacetylated salicylates, such as sodium salicylate and choline magnesium trisalicylate, are less potent *in vitro* inhibitors of cyclooxygenase (COX) than aspirin and appear to be associated with less gastrointestinal bleeding and fewer side effects but with comparable efficacy (87). A study performed with choline magnesium trisalicylate revealed an analgesic effect in malignant bone pain, although this did not reach statistical significance (88). COX-2 inhibitors are NSAIDS that can provide the anti-inflammatory therapeutic benefits of NSAIDS without significant side effects (88a). To date, human studies involving selective COX-2 agents have shown efficacy in rheumatoid and osteoarthritic pain and in acute dental pain (88b). Meloxicam is the first COX-2 inhibitor marketed in Europe. Celecoxib and rofecoxib (Vioxx) are both approved COX-2 inhibitors commercially available in the United States in 1999. NSAIDs are clearly the starting medications of choice for mild pain. However, if the pain becomes more severe or the toxicity profile becomes a concern, the patient should be started on an opioid.

OPIOID ANALGESICS

The mainstay of drug therapy for moderate-to-severe acute or chronic cancer pain are the opioids. With improved understanding of the clinical pharmacology of opioids, as well as wide clinical experience with their use, well-written guidelines are now available to all health care professionals and to the public (89). Reitera-tion of these guidelines is beyond the scope of this chapter. However, several points are extremely important and should be noted.

In general, for any patient with chronic pain, such as bone pain, the goal of treatment with opioids is to keep the patient comfortable and functional with as few side effects as possible. In treating chronic pain, oral administration is the best route because it is convenient, less expensive, and efficacious. Only full agonists are used, which include drugs such as morphine, oxycodone, hydrocodone, hydromorphone, methadone, fentanyl, and levorphanol. Partial agonists and mixed agonist-antagonists are never used in the treatment of cancer pain. Meperidine is also contraindicated because its metabolite normeperidine can accumulate and lead to a variety of neurological and psychiatric disturbances.

To achieve continuous pain relief without peaks and troughs, patients should be placed on sustained-release or long-acting opioids that treat the pain around the clock rather than on a p.r.n. basis. No opioid is inherently better than another, and with incomplete cross-tolerance the recommendation is sequential trials of different opioids with the hope of achieving adequate pain relief with minimal side effects. In changing from one opioid to another, it is very important to remember that there is equianalgesic dosing, with all of the different opioids being compared to 10 mg of parenteral morphine.

Bone pain not complicated by any neural involvement is a somatic pain, and is typically very responsive to opioids. Unlike NSAIDs, there is no ceiling dose with opioids, and the correct dose is the dose that treats the pain with minimal side effects. When opioids are used in a patient with pain, the side effects must be treated aggressively. Examples include the use of antiemetics for nausea and vomiting, use of neuroleptics for hallucinations, and placing patient on an aggressive bowel regimen, including a stool softener, such as docusate, and a largebowel stimulant such as senna. Tolerance develops to most opioid side effects except for constipation, which must always be treated in patients who are receiving opioids. If side effects become intolerable, a different opioid can be tried. Sometimes it is

essential to change from oral to parenteral or epidural/intrathecal administration, although this is not very common.

Two different types of problems can develop with bone pain that make it more difficult to treat. The first problem is that patients often experience both continuous pain and incident pain. Incident pain occurs when the patient moves the affected limb but is absent when the limb is at rest. Incident pain is usually the major limiting factor to activity (90). In a study done by Portenoy and Hagen (91), 63% of patients with controlled baseline pain had one or more episodes of breakthrough pain. To treat incident pain, Portenoy and Hagen suggest supplementing the basal regimen with opioids that have a rapid onset of action and a short duration immediately before the patient performs the activity that causes the pain. A relatively new formulation of oral transmucosal fentanyl citrate, which can produce analgesic blood levels of fentanyl within 5 minutes of placement in the oral mucosa, can be very helpful in the treatment of severe incident pain (92). In general, the recommended dose for the rescue opioid is 5–10% of the total daily dose (91). Even with such a small dose the patient may experience excessive sedation at rest. Psychostimulant drugs such as methylphenidate, dextroamphetamine sulfate, or caffeine can be added to the regimen to relieve some of the sedation. One study done with methylphenidate demonstrated that patients are less sedated and are able to tolerate higher doses of opioids (93).

The second problem arises when bone metastases invade neural structures and the patient develops a mixed somatic and neuropathic pain. When this occurs, the patient may require both opioids and adjuvant analgesics for neuropathic pain. Although a full discussion of neuropathic pain is beyond the scope of this article, some useful adjuvants include tricyclic antidepressants, anticonvulsants, oral local anesthetics such as mexiletine and flecainide, clonidine (Catapres), baclofen, N-methyl-D-aspartate antagonists such as ketamine HCl or dextromethorphan, and corticosteroids. To help prevent or relieve these difficult problems that may develop with bone metastases and bone pain, early use of radiotherapy as well as orthopedic and neurosurgical procedures is recommended.

CORTICOSTEROIDS

Even though only one placebo-controlled trial has been performed with corticosteroids in which oral methylprednisolone, 16 mg twice a day, was shown to be effective in relieving cancer pain (94), they are thought of as co-analgesics for both metastatic bone pain and neuropathic pain. In neurological emergencies, such as brain herniation or spinal cord compression, corticosteroids are used in high doses and may dramatically relieve headache and back pain (95). Corticosteroids may have beneficial effects in relieving bone pain by blocking the formation of leukotrienes and PGs via inhibition of COX and lipoxygenase enzymes. Corticosteroids may also be effective in reducing pain by decreasing peritumoral edema (96). Because the analgesic response of corticosteroids may be short-lived and because serious complications such as myopathies, immunosuppression, edema, pathological fractures, and delirium can develop, their use is usually limited to patients with neurological emergencies or those who have only days or weeks to live.

CALCITONIN AND GALLIUM NITRATE

Only small studies have been performed on the use of calcitonin and gallium nitrate in the treatment of bone pain. Calcitonin is a hormone that decreases blood calcium and inhibits osteoclastic bone resorption. In a small study using salmon calcitonin, 5 of 13 patients reported pain relief, whereas none of the 12 patients who received placebo had any pain relief (97). In another placebo-controlled trial in which eight patients with cancer pain received salmon calcitonin via lumbar puncture as well as weekly saline (placebo) injections, seven of the patients reported pain relief 15 minutes after receiving the injection via lumbar puncture, which lasted up to 48 hours, and in four patients the relief lasted up to 60 hours. The patients did experience side effects, which included nausea, vomiting, and diuresis. The fact that the patients experienced relief of pain when salmon calcitonin was given intrathecally supports the idea that its analgesic actions may not be related merely to its effect on bone, it may also act as a neurotransmitter in the central nervous system (98). The role of salmon calcitonin appears to be limited because it has a short duration of action and tachyphylaxis develops rapidly (99). Gallium nitrate, a potent osteoclast inhibitor, may have the potential to be useful as a co-analgesic. However, because the method of administration (a continuous 5-day i.v. infusion) is inconvenient and the risk for nephrotoxicity is high, its use appears unattractive (1).

BISPHOSPHONATES

Bisphosphonates—pyrophosphate analogues—are potent inhibitors of bone resorption. Although their mechanism of action is not completely understood, they are believed to exert their effects in several different ways. First, they may bind directly to bone and block dissolution of the mineral component. Second, they may inhibit osteoclast activity. Third, they may impair osteoclast chemotaxis to sites at which bone resorption is ongoing. Three bisphosphonate compounds have been studied for use in tumorinduced bone disease and bone pain. The three compounds, in order of increasing potency, are etidronate, clodronate, and pamidronate.

Oral bisphosphonates have also been studied. However, their place in the management of patients with cancer remains unclear. In general, the drugs' absorption when given orally is less than 5% of the administered dose and is variable. Concomitant ingestion of calcium, such as milk, can completely abolish their absorption. Patients may also have severe gastrointestinal intolerance to the medications. The bisphosphonates must be taken 1 or more hours before or after meals; this is difficult for patients who already have decreased appetite and other gastrointestinal complaints (100).

Most data concerning the roles of p.o. and i.v. bisphosphonates in pain control have been obtained with clodronate and pamidronate. A double-blind trial of oral etidronate, the least potent bisphosphonate, in 173 patients with multiple myeloma demonstrated its lack of efficacy in preventing the complications of metastatic bone disease (101). In a trial using 1600 mg of p.o. clodronate versus placebo, it was observed that, as measured by a visual analogue scale, there was a significant reduction of pain. What was not found was a significant reduction in analgesic use. Indeed, in both groups there were increases in the analgesic requirements (102). Similar results—a significant reduction of pain without a reduction in analgesic use—were reported when i.v. clodronate was studied (103).

In a prospective unblinded trial of 161 patients with metastatic breast carcinoma who received prolonged oral pamidronate, the incidence of hypercalcemia, bone pain, and symptomatic imminent fractures was reduced by 65%, 30%, and 50%, respectively. In this study, greater effects were seen in the patients who received pamidronate, 600 mg/day, versus 300 mg/day. However, the higher dosage could not be maintained because of gastrointestinal toxicity (104).

Several studies on the use of i.v. pamidronate in breast cancer and multiple myeloma have revealed a decrease in pain. In a placebo-controlled, randomized trial of 90 mg i.v. pamidronate versus placebo given as 12 monthly 2- hour infusions in addition to chemotherapy in 382 patients with metastatic breast carcinoma, there was a reduction in the occurrence of skeletal complications as well as a decrease in bone pain. The decrease in bone pain was seen after three, six, and nine cycles of pamidronate. At the final measurement, pain scores increased over baseline in both groups, but the increase was significantly greater in the placebo group. For patients with pain at baseline, 44% of pamidronate patients compared to 32% of placebo patients had a decrease in their pain score at the last measurement (105). Similar benefits were noted by Lipton et al. (106) in a study of 372 patients with metastatic breast carcinoma receiving hormonal therapy. Pain scores decreased from baseline for patients receiving pamidronate, whereas an increase was seen with placebo, and fewer patients receiving pamidronate required an increase in analgesic use than did the patients receiving placebo (30% vs. 43%). At the last measurement, the changes in baseline in the pain score, analgesic score, and Eastern Cooperative Oncology Group performance status were worse in the placebo group compared to the pamidronate group (106).

Symptomatic improvement in bone pain with the use of i.v. pamidronate has been reported at doses that may differ from those currently recommended. Glover et al. (107) and Lipton et al. (108) reported on the same doseranging study in breast cancer patients with bone metastases. Doses employed included 90 mg every 4 weeks, 60 mg every 4 weeks, 60 mg every 2 weeks, and 30 mg every 2 weeks. Reduction in bone pain by week 6 of treatment was noted with the 60-mg and 90-mg treatments. The 30-mg treatment was not effective. In a trial of pamidronate 45 mg every 3 weeks in patients with breast carcinoma, there was a prolongation to the time of progressive bone disease and improved bone pain (109). In a randomized, double-blind trial of pamidronate in multiple myeloma patients with at least one lytic lesion, quality of life assessments noted a significant decrease in bone pain from baseline, as well as no increase in analgesic use or deterioration in Eastern Cooperative Oncology Group performance status, in those who received pamidronate versus placebo (110). Thiebaud et al. (111) used 60 mg of pamidronate by continuous infusion in patients with painful bone metastases from multiple myeloma, lymphoma, and breast carcinoma. Symptomatic improvement in pain score was noted in eight of nine patients with multiple myeloma and in 9 of 18 patients with breast carcinoma. There also was a reduction in analgesic use and an increase in mobility (111).

Intravenous pamidronate has also been studied in patients with metastatic prostate carcinoma. In Lipton's study looking at patients with breast cancer and prostate cancer, there was some reduction in pain in prostate cancer, but not to the same degree as seen in the patients with breast cancer, and no dose-response relationship was evident (108). Clarke et al. (112) treated 25 patients with advanced prostate carcinoma over a 6-month period. During the first month of therapy, pamidronate, 30 mg, was given once weekly for 4 weeks and twice weekly for the next 5 months. Eleven of 17 patients with pain at the start of the study were pain-free after 6 months. These authors concluded that pamidronate may be effective in palliating bone pain in some patients with prostate carcinoma. However, further controlled trials should be conducted.

There is some evidence with i.v. clodronate, and even more evidence with i.v. pamidronate, that the bisphosphonates can potentiate the effects of analgesics in the treatment of bone pain from bone metastases. However, the effect is modest and there is not a significant decrease in analgesic consumption. Newer, more potent bisphosphonates are being developed for clinical use and may prove to be beneficial in the treatment of bone pain. One example is zoledronic acid, a new-generation highpotency bisphosphonate. A recent phase II trial was undertaken in which patients with metastatic breast cancer or multiple myeloma were randomized to doubleblind treatment with either 0.4 mg, 2.0 mg, or 4.0 mg of zoledronic acid or 90 mg pamidronate. Among the 232 patients with pain at study entry, a decrease in pain score was reported by a greater proportion of patients in the 4.0 mg zoledronic acid group (67%) than in the 0.4 mg, 2.0 mg, and pamidronate groups (51%, 48%, and 50%, respectively), not statistically significant. Similarly, a decrease in analgesic score among patients taking pain medications was reported for 27% of patients in

the 4.0 mg zoledronic acid group, compared to 19%, 11%, and 21% of patients in the 0.4 mg and 2.0 mg zoledronic acid groups and the pamidronate group (112a).

INVASIVE INTERVENTIONS

In the treatment of cancer-related pain, invasive interventions such as neural blockade, neurosurgical procedures, or epidural and spinal analgesia are usually undertaken when the pain is either resistant to other modalities or when there are intolerable side effects from the treatments that are being used. Neural blockade may be efficacious when the pain is well localized. Local anesthetics can be injected in various locations including the brachial plexus, lumbar sympathetic plexus, and pleural cavity. Depending on the concentration of the local anesthetic, either afferent blockade or afferent and motor blockade can be obtained. When the pain is not well localized and is innervated by multiple nerves, intraspinal analgesia is more appropriate than neural blockade. Intraspinal analgesia usually involves use of opioids, local anesthetics, and/or clonidine.

A new technique that has shown some promise in the treatment of metastatic bone lesions is radiofrequency ablation (RFA). RFA is a treatment that has been traditionally used for treatment of intractable back pain due to failed back syndrome, and chronic back pain due to facet joint osteoarthritis as well as for the treatment of osteoid osteomas (112b). A preliminary study using CT-guided RFA revealed that subjective pain relief can be obtained in patients with metastatic bone tumors that remain painful after radiation therapy or are solitary and can be treated without subjecting the bone marrow to immunosuppressive doses of external beam radiation therapy (112c). Currently, this is a potentially innovative and cost effective treatment that is being studied at both the National Institutes of Health and nationally in a phase II design.

The most invasive procedures, with significant irreversible side effects, include neuroablative procedures. These procedures are performed only when a patient has both intractable pain and a limited life expectancy. The two procedures that have been used for bone pain include percutaneous cordotomy and pituitary ablation. Percutaneous cordotomy involves interruption of the ascending spinothalamic tract and is a possibility when there is unilateral pain, especially of the lower limbs. Possible complications include paresis and bladder dysfunction. There is also a risk that patients may develop pain above or below the level of analgesia, or even at the opposite side of the body. With bilateral cordotomy, there is a significant risk for respiratory failure. There is a potential role for pituitary ablation in patients with hormone-responsive tumors and widely metastatic bone disease. Although the success rate has been quoted as high as 74– 94%, long-term follow-up has not been performed with these patients. In addition, the procedure involves significant complications, including meningitis, visual disturbances, diabetes insipidus, headaches, hypothalamic disturbances, and death. Clearly, before any invasive procedure is undertaken the risks must be measured against the potential benefits (1).

CONCLUSION

In addition to the already discussed treatments, physiatry, including bracing, prostheses of various types, wheelchairs, and both physical therapy and occupational therapy, is critical in improving pain, ambulation, and quality of life in patients with bone metastases and bone pain. In addition, it is essential to address issues such as depression, anxiety, and spiritual concerns in patients who have bone pain and metastatic disease that they know is not curable. The suffering component of the total pain picture must be addressed to achieve relief from pain. Cancer pain, including bone pain, can usually be effectively managed if one does a comprehensive assessment and develops a multimodality treatment plan.

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3

OPIOID PHARMACOTHERAPY

RICHARD PAYNE

PHARMACOTHERAPY OF PAIN: BASIC PRINCIPLES

Advances in pain management techniques have made it possible to provide adequate control for the vast majority of patients with cancer, acquired immunodeficiency syndrome, and other chronic medical disorders using relatively simple means. Unfortunately, pain often remains inadequately treated for cancer and many other illnesses (1). Several factors contribute to the undertreatment of cancer pain, including poor physician assessment, inadequate knowledge of management techniques (including pharmacotherapy measures), and negative physician and patient attitudes towards the use of opioids for pain (2).

In a large, prospective study, physicians identified inadequate pain assessment as the primary reason for poor pain management (2). Successful management of pain in the cancer patient begins with a thorough assessment of the pain complaint. Adequate pain assessment includes the documentation of pain intensity and quality and the evaluation of exacerbating and relieving factors, and requires knowledge of the common pain syndromes occurring in a specific disease or disorder. Principles of pain assessment are covered elsewhere in this book and by other references (1).

Treating the cause of pain should be a high priority for the clinician. For example, in one study, 18% of cancer patients evaluated by a pain service required additional antineoplastic therapies to treat their pain (3). Recently, two chemotherapeutic agents, gemcitabine hydrochloride (4) and mitoxantrone hydrochloride (5), were approved by the U.S. Food and Drug Administration for the palliative treatment of pancreatic cancer and hormone-refractory prostate cancer, respectively. Similarly, radiotherapy is effective in relieving metastatic bone pain. For localized bone pain, external beam treatment reduces pain in up to 80% of patients (6). More pertinent to the subject of pharmacotherapy, the administration of systemic radio-isotopes such as strontium-89 has also been shown to be effective in treating diffuse pain from bone metastases (7). However, pain relief with strontium-89 may not be seen until the third or fourth week after treatment, although it may be sustained for several months (7).

Pharmacotherapy must be individualized to maximize pain relief and minimize adverse effects. The World Health Organization (WHO) has developed a three-step analgesic ladder for the treatment of cancer pain (8), which serves as a model paradigm for pharmacotherapy approaches to pain management (Fig. 3-1).

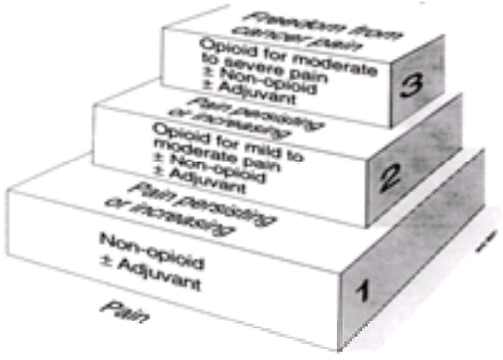

FIGURE 3-1. World Health Organization analgesic ladder. (From World Health Organization. *Cancer pain relief and palliative care: report of a WHO expert committee*, 3rd ed. Geneva, 1996, with permission.)

The WHO approach advises clinicians to match the patient's reported pain intensity with the potency of the analgesic to be prescribed. For mild pain, one should administer a nonopioid drug such as acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID), unless contraindicated (Table 3-1). For moderate pain that cannot be controlled by an NSAID alone, a so-called “weak” opioid such as codeine phosphate or hydrocodone bitartrate should be administered, often in a fixed combination with aspirin, another NSAID, or acetami-nophen (Table 3-2). For severe pain, a so-called “strong” opioid drug such as morphine sulfate, hydro-morphone, methadone hydrochloride, or fentanyl should be administered (Table 3-2). NSAIDs and adjuvant analgesic drugs (see the section Adjuvant Analgesics in Cancer Pain Management) can be administered at any stage of the WHO ladder. It is important to note that patients presenting with severe pain should not be walked up the ladder starting from the first step, which is a common mistake, but should be administered a strong opioid immediately. Cleeland et al. (9) reported that 46% of ambulatory cancer patients were under-treated for pain as measured by a tool called the “pain management index.” The pain management index is based on the WHO analgesic ladder, and relates the potency of the analgesic regimen prescribed to the patient's reported pain intensity, assigning negative values (indicating undertreatment) when the pain intensity is not matched by an appropriate analgesic class, as often happens when patients with severe pain are inappropriately started on the first or second step of the analgesic ladder. The WHO analgesic ladder approach has been validated (10). However, many of the validation studies have been criticized because they have not included prospective evaluation of individual patient outcomes (11). Nonetheless, the WHO analgesic ladder approach remains the standard method for prescribing pharmacotherapies for pain.

Drug type	Name/ brands	Typical starting dose
Acetaminophen	Tylenol and others	650 mg q4h p.o.
Aspirin	Multiple	650 mg q4h p.o.
Ibuprofen	Motrin and others	200–800 mg q6h p.o.
Choline magnesium trisalicylate	Trilisate	1000–1500 mg three times daily p.o.
Diclofenac sodium	Voltaren	50–75 mg q8–12h p.o.
Diflunisal	Dolobid	500 mg q12h p.o.
Etodolac	Lodine	200–400 mg q8–12h p.o.
Flurbiprofen	Ansaid	200–300 mg q4–8h p.o.
Naproxen	Naprosyn	250–750 mg q12h p.o.
Naproxen sodium	Anaprox	275 mg q12h p.o.
Oxaprozin	Daypro	600–1200 mg q daily p.o.
Sulindac	Clinoril	150–200 mg q12h p.o.
Piroxicam	Feldene	10–20 mg q daily p.o.
Nabumetone	Relafen	1000–2000 mg q daily p.o.
Ketoprofen	Orudis	50 mg q6h p.o.
Ketorolac tromethamine	Toradol	10 mg q4–6h p.o. (not to exceed 10 d??)
Ketorolac tromethamine	Toradol	30 mg i.m. or i.v. × 1 then 15 mg i.m. or i.v. q6h (not to exceed 5 d)

TABLE 3-1. PARTIAL LIST OF ACETAMINOPHEN AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS USED FOR CANCER PAIN

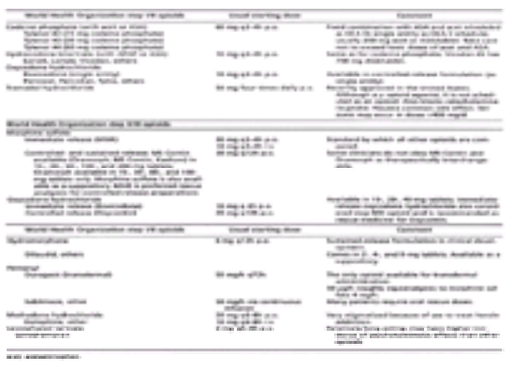

TABLE 3-2. COMMONLY USED OPIOIDS FOR CANCER PAIN

Acetaminophen and Nonsteroidal Anti-Inflammatory Analgesics

The basic principles of pain assessment and management apply when using acetaminophen and NSAIDs (Table 3-3). The NSAIDs constitute a large class of compounds that have analgesic, anti-inflammatory, and antipyretic effects. Of course, aspirin is the prototype drug in this class. Many of these analgesics are available over the counter; a 1995 survey in the *Wall Street Journal* estimated the sales of acetaminophen and NSAIDs to be more than $3 billion in the United States alone, with Tylenol brand of acetaminophen producing almost $800 million in sales alone.

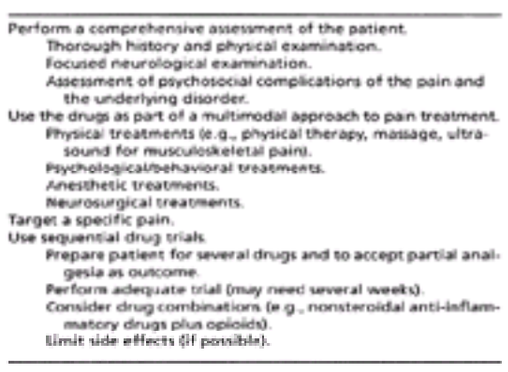

TABLE 3-3. BASIC PRINCIPLES IN USE OF NONOPIOID DRUGS

Acetaminophen is considered to be in this class, although it has only weak anti-inflammatory potency (12). Acetaminophen and NSAIDs constitute the first line of management in the pharmacotherapy of acute and cancer pain, as recommended by the WHO guidelines (8) and the Agency for Health Care Policy and Research acute pain and cancer pain clinical practice guidelines (13,14). Although widely used by consumers and patients, NSAIDs are seldom the sole agents used to treat pain and are therefore more often part of a multimodal approach to management.

NSAIDs and acetaminophen have a ceiling effect to their analgesic efficacy such that increasing the dose beyond this level produces no increase in therapeutic effect, although it may produce more side effects (15). Therefore their use as sole agents in the management of pain should be restricted to mild or moderate pain because severe pain is often above their ceiling dose for analgesic efficacy.

The minimum effective dose and the ceiling dose of NSAIDs may vary among individuals, however, so that some dose titration may be necessary within a narrow range of doses (15,16). Because patients vary in their response to NSAIDs, a trial of an alternative drug in the same class may be justified if side effects outweigh benefits for a particular drug (16).

The NSAIDs inhibit cyclooxygenase, thereby inhibiting prostaglandin synthesis (17). Prostaglandins are important mediators of the inflammatory process that may serve to activate and sensitize nociceptors; NSAIDs appear to produce analgesia by this peripheral action on prostaglandin inhibition (16). However, recent data also indicate that NSAIDs have a central nervous system (CNS) site of action at the brain or spinal cord level that is important for their analgesic effects (18).

Recently, two isoforms of the enzyme cyclooxygenase (COX-1 and COX-2) have been demonstrated (19). The COX-1 isoenzyme is normally found in blood vessels, stomach, and kidney, whereas COX-2 is induced in peripheral tissues by inflammation. Inhibition of COX-1 is associated with the well-known gastric and renal side effects linked with NSAID use, whereas COX-2 inhibition produces therapeutic effects (Fig. 3-2).

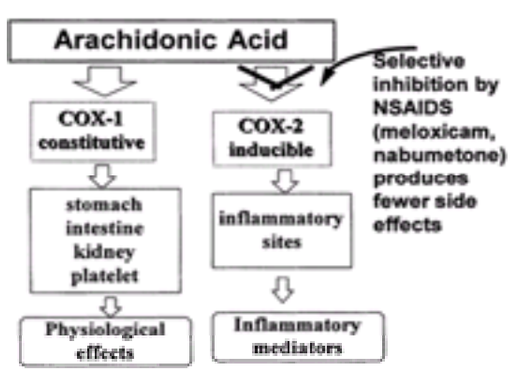

FIGURE 3-2. Cyclooxygenase (COX) inhibitors. NSAIDS, nonsteroidal anti-inflammatory drugs.

Most NSAIDs nonselectively inhibit the COX isoenzyme, thereby producing toxic and therapeutic effects. Relatively selective COX-2 inhibitors such as meloxicam and nabumetone have been shown to have fewer gastrointestinal (GI) and renal side effects (20).

Acetaminophen is equipotent to aspirin in terms of analgesic efficacy, is generally very well tolerated, and is not associated with the risks of GI hemorrhage that are linked with NSAID use. Acetaminophen is a weak inhibitor of COX, which presumably explains its poor antiinflammatory potency. This analgesic is the principal metabolite of phenacetin, which is a known nephrotoxin. Renal failure has been described with long-term use of acetaminophen (21), in addition to its well-known hepatotoxicity. Acute hepatotoxicity occurring during overdose is correlated with acetaminophen plasma concentrations above 200 mg/ml at 4 hours after ingestion, or if plasma concentration persists above 10 mg/ml at 24 hours after ingestion (22). Although not as well correlated with plasma concentrations, it is well known that chronic ingestion of acetaminophen ranging from 2.5 to 4.0 g/day increases the risk for hepatotoxicity (21). In addition, the odds of chronic renal failure have been shown to be doubled for patients who have a cumulative lifetime intake of more than 1000 pills of acetaminophen (21). NSAID and acetaminophen use is relatively safe, but these data, combined with the well-known risks of GI bleeding and platelet dysfunction that occur with acute and chronic NSAID use, indicate that these drugs should be used judiciously.

Many NSAIDs are now available. They differ in dosing interval and cost, and to some extent, in their analgesic ceiling and safety. The choice of NSAID must be individualized to the patient's needs (Table 3-1). Ketorolac tromethamine is available in an oral and parenteral formulation; it is currently the only NSAID available in both an intramuscular and intravenous formulation. This NSAID is used often in hospitalized patients to manage postoperative pain and other acute pains, including

exacerbations of chronic cancer pain and sickle cell pain. Another use of ketorolac tromethamine is in acutely ill patients experiencing side effects such as opioid-induced ileus or delirium, in which the addition of a parenteral NSAID often has an important opioid-sparing effect to allow dose reduction and the lessening of GI and CNS side effects of opioids without compromising analgesia.

Several studies have confirmed the effectiveness of the NSAIDs in the treatment of cancer pain (23,24). Of interest, prior studies that documented the additive analgesic effects of NSAIDs when combined with opioids in singledose postoperative pain studies (27) have not been confirmed in a more recent meta-analysis of repeated dose studies (24). This is puzzling because NSAIDs and opioids have different mechanisms of action and logically could have additive analgesia. Furthermore, much anecdotal clinical practice suggests that additive analgesic effects do occur when NSAIDs and opioids are coadministered (8), and it is still common clinical practice to use NSAIDs and opioids in combination despite the findings of the more recent meta-analysis.

Certain adverse effects are common to most of the drugs in this group. All may be associated with GI toxicity, with the most serious complications being ulceration and bleeding. A meta-analysis of the risks of GI toxicity associated with NSAID use compared 12 studies (25). Ibuprofen in doses less than 1600 mg/day was associated with the least risk for serious GI hemorrhage; aspirin, indomethacin, naproxen, and sulindac were associated with intermediate risk, and ketoprofen and piroxicam were highest risk (25).

NSAIDs also inhibit platelet function to a variable degree; aspirin is the strongest platelet inhibitor, whereas the nonacetylated salicylates, such as choline magnesium trisalicylate, have minimal effects on platelets (26). However, all NSAIDs must be used with caution in patients with coagulopathies and coexisting GI pathology, and when coadministered with drugs that also have GI toxicity (e.g., corticosteroids). Another relative contraindication to the use of NSAIDs relates to their antipyretic effects, which may mask fever as an early sign of serious infection in immunocompromised patients.

Commonly Used Opioids for Pain Management

Because opioids alter the unpleasant emotional experience associated with nociception and provide pain relief by interacting with specific receptors (28), they are essential components in the pharmacotherapy of pain (8,13,14). Drugs that bind to opioid receptors are classified as *agonists* (e.g., morphine sulfate) if they produce analgesia. Opioids are classified as *antagonists* (e.g., naloxone hydrochloride) if they block the action of an agonist. *Agonist-antagonists* (e.g., pentazocine hydrochloride) are opioids that produce analgesia by interacting with a specific receptor (e.g., k) but also bind to other receptors (e.g., μ), where they can block the action of an agonist. *Partial-agonist opioids* (e.g., buprenorphine hydrochloride) bind to receptors and produce analgesia, but unlike morphine sulfate they exhibit a ceiling effect: Increases in doses do not parallel increases in analgesia (16).

As noted above, the WHO analgesic ladder paradigm classified opioids as “weak” or “strong” depending on their relative efficacy in relieving pain (8), although this concept of distinguishing weak and strong opioids has been challenged, and some have even advocated the elimination of the second step of the WHO analgesic ladder (29). The so-called “weak” opioids are used for less severe pain because their efficacy is limited by an increased incidence of side effects at higher doses (e.g., nausea and constipation with codeine phosphate, CNS excitation with propoxyphene). Furthermore, these weak opioids are usually formulated as a fixed oral dose mixture with a nonopioid analgesic so that their efficacy is limited also by the maximum safe daily dose of acetaminophen (4 g/day) or aspirin. By contrast, so-called “strong” opioids are used for severe pain. Opioids such as morphine sulfate, hydromorphone, fentanyl, methadone hydrochloride, and levorphanol tartrate have a relatively wide therapeutic window and no ceiling effect for analgesia-increasing doses. They produce a greater level of analgesia with a lesser likelihood for dose-limiting side effects than the weak opioids. However, as noted below, the management of side effects is critical to achieving optimal results with the administration of opioids in either class.

Codeine phosphate, the demethylated congener of morphine sulfate, is the prototype of the weak or step II opioid analgesics. Although a parenteral preparation is available, codeine phosphate is nearly always given by mouth, often in a fixed mixture with a nonopioid analgesic. A 200-mg dose is equipotent to 30 mg of morphine sulfate (30). The half-life of codeine phosphate is 2.5–3.0 hours; approximately 10% of orally administered codeine phosphate is demethylated to morphine sulfate, and free and conjugated morphine sulfate can be found in the urine. The analgesic action is thought to be related to the *in vivo* conversion to morphine sulfate (30). Constipation and nausea are the most common side effects at the usual therapeutic doses of codeine phosphate (30–60 mg every 4 hours). Codeine phosphate is useful to administer as an alternative to NSAIDs for patients with mild pain in whom the antipyretic, antiplatelet, or GI toxicity of NSAIDs contraindicate their use.

Hydrocodone bitartrate is a codeine phosphate derivative available only in combination with acetaminophen or aspirin. At the usually prescribed doses, its analgesic effect is weak and probably only slightly superior to acetaminophen alone.

Two opioids classified as weak or WHO step II analgesics, meperidine hydrochloride and propoxyphene, although widely used for the treatment of acute and chronic pain, are not generally recommended by pain clinicians.

Propoxyphene is a synthetic analgesic that is structurally related to methadone hydrochloride. It is approximately equipotent to codeine phosphate. Although its analgesic effect lasts only 3–6 hours, the plasma half-life is as long as 6–12 hours. This disparity between the relatively short analgesic duration of effect in comparison to the longer plasma half-life is similar to that of methadone hydrochloride, and patients are at significant risk for sedation and increased toxicity due to drug accumulation when it is dosed according to the analgesic duration of effect. Furthermore, propoxyphene has norpropoxyphene as its major metabolite; norpropoxyphene has a long plasma half-life of 30–36 hours and may also be responsible for some of the observed toxicity (31). Norpropoxyphene has local anesthetic effects similar to those of lidocaine and high doses may cause arrhythmias. Seizures occur more often with propoxyphene intoxication than with opiate intoxication. Naloxone hydrochloride antagonizes these toxic effects of propoxyphene (31).

Meperidine hydrochloride is an opioid agonist. The dose equianalgesic to 10 mg of parenteral morphine sulfate is 75–100 mg. The reasons for its widespread use in the treatment of pain is unclear. Although often cited as a reason to use meperidine hydrochloride in preference to morphine sulfate, the lesser rise in pressure in the common bile duct with meperidine hydrochloride administration has not been shown to be clinically advantageous (32). Furthermore, the CNS excitatory effects that appear after chronic use are well substantiated and occur as a result of the accumulation of the metabolite normeperidine, which causes multifocal myoclonus and grand mal seizures (33). The normeperidine toxicity is correlated with plasma concentration and is probably not opioid receptor-mediated because it is not reversed by naloxone hydrochloride. The half-life of meperidine hydrochloride is 3 hours. Normeperidine has a half-life of 15–30 hours and therefore accumulates with repetitive dosing of meperidine hydrochloride, particularly in patients with renal dysfunction. Meperidine hydrochloride also has an important drug interaction with monoamine oxidase inhibitors, which produces two patterns of toxicity: (a) severe respiratory depression, or (b) excitation, delirium, hyperpyrexia, and convulsions. This toxicity may lead to fatalities.

Oxycodone hydrochloride is a semisynthetic opioid. Because of its high bioavailability (>50%) after oral dosing, it is a useful opioid analgesic (33). It has a half-life of 2–3 hours and a duration of action of 4–6 hours. It is metabolized by demethylation and conjugation in the liver, in a manner similar to codeine phosphate, and is excreted in the urine (34). Part of the analgesic action is mediated by active metabolites. Traditionally, oxycodone hydrochloride has been considered a weak or WHO step II analgesic because it is most often used in a fixed combination with acetaminophen and aspirin. These combinations limit its dose to 10 mg every 4 hours. However, oxycodone hydrochloride can also be prescribed as a single-entity compound, and as such it is often used as a WHO step III or strong opioid (35,36), especially now that it is available in a sustained-release formulation. Therefore, oxycodone hydrochloride straddles the second and third steps of the WHO analgesic ladder, depending on which formulations are used. Oxycodone hydrochloride has been reported to have fewer side effects than morphine sulfate (36,37), although these studies have limitations to their interpretation because they were not done in a rigorous study design in which patients were blinded to the specific drugs being administered. Like morphine sulfate, the availability of oxycodone hydrochloride in sustained- and immediate-release formulations provides a means for the clinician to carefully titrate the dose of drug to the patient's response.

Morphine sulfate is, of course, the prototype opioid agonist. The WHO has designated morphine sulfate as the “drug of choice” for the treatment of severe pain associated with cancer (8). The half-life of morphine sulfate is approximately 2 hours, and oral immediate-release morphine sulfate preparations generally provide pain relief for 2–4 hours. Slow-release preparations that permit once- or twice-a-day regimens are safe and effective; they are generally best used after dose titration with immediate-release morphine sulfate.

Recently, morphine sulfate has been shown to have active metabolites. Morphine sulfate is metabolized in the liver, where it undergoes glucuronidation at the 3 and 6 positions. Morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) accumulate with chronic morphine sulfate administration (38). M6G binds to μ receptors with affinity similar to that of morphine sulfate (39). M6G appears to be 20 times more potent than morphine sulfate when administered directly into the periaqueductal gray (39), indicating that only a fraction of this water-soluble metabolite need cross the blood–brain barrier to produce an analgesic effect (38). In single-dose comparative analgesic trials, the parenteral to oral relative potency ratio for morphine was shown to be 1:6 (27). Chronic morphine sulfate dosing has been shown to produce a parenteral to oral relative potency ratio of 1:3 (40); this difference is likely due to the presence of the M6G metabolite.

Although the M3G metabolite has a negligible affinity for opioid receptors and does not produce analgesia (39), it may be responsible for some of the toxicity seen with chronic dosing of morphine sulfate, especially when relatively large doses are administered. The M3G metabolite has excitatory effects on neurons and can cause myoclonus and possibly a hyperanalgesic state (41,42), paradoxically causing increased pain. Morphine sulfate metabolites are eliminated by glomerular filtration; they accumulate in renal failure, leading to an increased incidence of side effects (43). Morphine sulfate should be used with caution in renal failure, with an increase in the

interval time between doses. Hydromorphone is another semisynthetic opioid agonist commercially available as a highly water-soluble salt. When administered parenterally, 1.5 mg of hydromorphone is equipotent to 10 mg of morphine sulfate. Its bioavailability is 30–40% when given orally, and the oral to parenteral relative potency ratio is 5:1 (44). Hydromorphone has a half-life of approximately 2 hours. Recently, a 3-0 methyl metabolite of hydromorphone has been measured, which may be responsible for analgesic effects and toxicity such as myoclonus that occurs with continuous high-dose hydromorphone administration (45). Because of its availability in a high-potency formulation (10 mg/ml) and its water solubility, hydromorphone is the drug of choice for the chronic subcutaneous route of administration (44).

Levorphanol tartrate is a synthetic potent μ opioid agonist that also binds d and k receptors (46). This k receptor binding may explain its relatively high prevalence of psychotomimetic effects (e.g., delirium, hallucinations) in comparison to other opioids when given to patients. When administered parenterally, 2 mg of levorphanol tartrate is equianalgesic to 10 mg of morphine sulfate (46). This opioid has a half-life of 12–30 hours and a duration of analgesia of 4–6 hours (47). As is the case with other opioids in which the plasma half-life exceeds the duration of analgesia, repeated administration is associated with drug accumulation. Therefore, a dose reduction may be required 2–4 days after commencement of the drug to avoid side effects from overdose. For the same reason, it is best to avoid this opioid in patients with impaired renal function or encephalopathy. Levorphanol tartrate is used as a second- or third-line drug in patients who cannot tolerate morphine sulfate, hydromorphone, or fentanyl.

Methadone hydrochloride is a synthetic μ opioid agonist with high oral bioavailability (49). When administered orally, it is rapidly absorbed from the GI tract with measurable plasma concentrations within 30 minutes after oral administration (49). When administered in single parenteral doses it is equipotent to morphine sulfate; the duration of analgesia is 4–6 hours (49).The plasma level declines in a biexponential manner, with a half-life of 2–3 hours during the initial phase and 15–60 hours during the terminal phase (50). This biexponential decline accounts for the relatively short analgesic action and the tendency for drug accumulation with repeated dosing. A reduction in dose and interval frequency is often needed during the first days of treatment to prevent side effects from overdose (51). Methadone hydrochloride is an effective second-line drug for patients who experience unrelieved pain and intolerable side effects with morphine sulfate (54,55).

Because of the large disparity between the plasma half-life and the analgesic duration of effect, dosing recommendations for methadone hydrochloride are complex. For example, it has been recommended to use a tenth of the daily morphine sulfate dose as the starting methadone hydrochloride dose, but not to exceed 100 mg, and to give this dose at intervals to be determined by the patient (but not more frequently than every 3 hours) (55). The calculated equianalgesic doses of methadone hydrochloride may be as little as 3% of the predicted dose when this opioid is administered chronically (56).

Methadone hydrochloride is an alternative to morphine sulfate in several circumstances. Because of its low cost, it is an attractive alternative to morphine sulfate. It should also be considered for the rare patient who is allergic to morphine sulfate because its very different chemical structure makes cross-sensitivity less likely than with other opioids, such as hydromorphone or oxycodone hydrochloride. The pharmacokinetics of methadone hydrochloride can be influenced by impaired renal clearance and decreased plasma protein binding. Methadone hydrochloride is excreted almost exclusively in the feces; it has been proposed as a safe and effective analgesic for patients with chronic renal failure (57).

Fentanyl is a very potent synthetic, lipophilic μ opioid agonist (58). It is 80–100 times more potent than morphine sulfate. These properties allow this opioid to be administered by the transdermal route (58). A special rate-controlling membrane provides additional control of drug release, although the kinetics of the transdermal fentanyl system can be altered by fever and obesity of the patient. The transdermal absorption of fentanyl is the same from chest, abdomen, and thigh (58). A skin reaction at the application site is found in 4% of patients (58). After application of the transdermal patch the systemic absorption is negligible for the first 4 hours, and then increases steadily from 8 to 24 hours (59). Patients reach steady-state concentrations within 12–24 hours from the application (60,61). After removal of the transdermal patch, the serum fentanyl concentration falls approximately 50% in approximately 16 hours (61). This apparently long half-life is likely due to the slow washout of fentanyl from cutaneous reservoirs and mobilization of this lipophilic drug from fat stores (61). These pharmacokinetic considerations translate clinically in a severalhour delay in the onset of analgesia after an initial application and a persistence of analgesia and eventual side effects long after removal of the transdermal system. In patients with chronic pain, it is possible to obtain relatively constant serum fentanyl concentrations comparable with continuous intravenous or subcutaneous infusions after a variable period of titration (61). More recently, the use of oral transmucosal fentanyl has been proposed for the treatment of breakthrough pain (64). Fentanyl can be formulated in a syrup-candy matrix that can be sucked. This fentanyl oral formulation can provide analgesic fentanyl blood concentrations within 5–10 minutes of active sucking, with a peak effect in 20–30 minutes and a duration ranging from 1 to 4 hours (64). Oral transmucosal fentanyl has recently been approved for the treatment of breakthrough pain, which is defined as acute transient exacerbations of pain on a baseline of otherwise controlled chronic pain (65).

Intraspinal Administration of Analgesics

Opioid analgesics can be introduced into the epidural or intrathecal space for the management of pain in selected patients with cancer pain. Small doses of opioids administered by these routes are delivered in close proximity to their receptors in the dorsal horn of the spinal cord, thus achieving high local concentrations. Because the amount of drug administered is reduced, these routes of delivery may produce good analgesia with fewer of the side effects associated with equianalgesic doses of systematically administered opioids (83). Spinally administered opioids should be considered for patients whose pain is at least partially opioid-responsive but who cannot tolerate the side effects of oral or parenteral opioids, especially if attempts at managing these side effects have been unsuccessful.

Adverse effects of spinal opioids are thought to result in part from supraspinal redistribution of drug, and include pruritus, urinary retention, nausea, vomiting, and respiratory depression (83). Respiratory depression may occur early (1–2 hours) or late (6–24 hours), but the risk of respiratory depression in patients who are not opioid-naïve is quite low. Tolerance to the analgesic effects of spinal opioids may develop rapidly in some patients, possibly limiting the usefulness of this route of administration in some individuals (83).

When a patient is considered a potential candidate for spinal opioids, an initial trial of opioid administered through a temporary epidural or intrathecal catheter is recommended. If the individual's response to spinal opioids is sufficient to warrant more prolonged therapy, the temporary catheter should be replaced with a permanent implanted catheter to reduce the risks of infection and catheter migration (84). A number of implanted drug delivery systems are available for both epidural and intrathecal administration of opioids. The opioid may be delivered by intermittent bolus or by continuous infusion; the two methods are equally efficacious (85). Catheter placement is associated with a low but definite risk of epidural infection. Nevertheless, long-term epidural analgesia is safe and effective when patients are monitored carefully and receive prompt treatment if signs of infection develop (86). When spinal opioids are considered for the treatment of back pain in the cancer patient, magnetic resonance imaging of the spine should ideally precede placement of an epidural catheter. This precaution avoids the potential for unexpected neurological deterioration from injection in the presence of epidural tumor (83). Coadministration of local anesthetics such as bupivacaine hydrochloride (0.025% concentration) with opioids into the epidural space may also enhance analgesia in selected cases and may be useful when opioid tolerance develops (86).

Practical Clinical Guidelines for Opioid Use

The onset, peak, and duration of analgesia vary with the opioid drug, the route of administration, and the particular patient. The recognition of this variability allows the appropriate choice of drug, route, and scheduling. When switching from one opioid to another, one-half of the calculated equianalgesic dose is recommended as the initial dose for titration (1,8,13,14).

Oral administration is recommended in most patients because it is convenient, well tolerated, and usually the least expensive method (8,14). However, transdermal administration of fentanyl has the advantage of convenience and long duration of action, and may improve patient compliance by deemphasizing the need to take something by mouth on a regular basis. However, most patients who take transdermal fentanyl require an oral or transmucosal rescue dose for breakthrough pain. All opioids should be titrated to effect, with intravenous boluses repeated every 15 minutes if necessary, until either analgesia or intolerable side effects develop, and oral doses of an immediate release morphine sulfate or oxycodone hydrochloride preparation as often as every 1–2 hours as need. The concomitant use of NSAIDS, antiemetics, and other coanalgesics is often warranted (8,14).

When pain is continuous, as is often the case, medications should be administered on an around-the-clock basis (8,14,16). Administering medications on an asneeded (p.r.n.) basis often results in the patient experiencing multiple episodes of pain during the day, and so is generally undesirable. However, p.r.n. administration is highly desirable for the first 24–48 hours after initiation of opioid therapy to determine the 24-hour dose requirement. If patients are started on an around-the-clock regimen and the starting dose is too high, unnecessary sedation and other side effects may occur, thereby reinforcing negative attitudes about taking opioids on the part of the patient. Once the optimum 24-hour dose is determined, the opioid should be prescribed by the clock. Many patients continue to experience “breakthrough pain,” or transitory increases in pain above its baseline level (65). For such pain, p.r.n. “rescue dose” of a shortacting opioid should be available, starting at 10–20% of the total scheduled daily dose.

There is enormous inter-individual variation in the dose that is necessary to provide adequate analgesia, even among patients with similar pain syndromes. The variability in opioid responsiveness is caused by pharmacokinetic and pharmacodynamic factors (66). Genetic factors such as race and gender have also been shown to be important in determining opioid responsiveness (67). For example, 15% of whites lack the oxidative phosphorylative enzyme CYPD211 needed to metabolize codeine phosphate to morphine sulfate *in vivo* and thereby require higher doses of codeine phosphate than do patients with normal metabolism (67). Kaiko et al. (68) noted that black and Asian patients participating in single-dose clinical trials to determine opioid efficacy reported twice the analgesic effect as whites in a retrospective analysis of the variations in opioid responsiveness. In another important recent study, Levine et al. (69) demonstrated that women achieved greater analgesia than men

when administered k opioid agonist drugs.

Patients on chronic opioid therapy often require relatively large dose increments to control acute exacerbations of pain. An infusion pump with a device for self-administration of extra doses of medication every few minutes (patient-controlled analgesia, PCA) should be used, if available (70). The PCA dose can be as high as the hourly rate during the titration phase and when incident pain is a concern. The continuous basal rate should be frequently adjusted based on the patient's report and the PCA usage. When venous access is problematic the subcutaneous route should be used. Once the acute pain exacerbation is controlled the medication should be changed to the oral or transdermal route. Long-term intravenous and subcutaneous opioid administration can be used in patients outside of the hospital; intravenous administration is only possible when long-term access is obtained through a central venous line (71,72).

Management of Side Effects of Opioid Analgesics

Constipation is the most common adverse effect of opiates. Tolerance to the constipating effects does not usually develop. Opioids cause constipation by a variety of mechanisms: decreased gastric, biliary, pancreatic, and intestinal secretions, and a decrease in the propulsive motility of stomach and intestine resulting in delayed passage of increasingly viscous stool. Central and peripheral opioid receptor mechanisms are implicated (73). A prophylactic laxative regimen must be instituted at the same time the opioid is started and maintained for the duration of opioid therapy.

Nausea and vomiting related to opioid administration is thought to be caused by direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla (31). Nausea can also be caused by an increased vestibular sensitivity or delayed gastric emptying. A vestibular component is suggested by the fact that nausea is uncommon in recumbent patients but occurs in 40% of ambulatory patients after 15 mg of parenteral morphine sulfate (31). It is still unclear whether these effects involve specific opioid receptors because it has not been established as to whether they are reversed by naloxone hydrochloride (31). Tolerance to this effect is the rule, and generally the nausea subsides in 2–3 days. M6G may be implicated in some patients with protracted nausea (74). Inadequately treated constipation can be a cause of persistent nausea.

Transient sedation is very common when opioid therapy is initiated (75). Opiate-induced sedation must be differentiated from the predictable deep sleep that follows pain relief in sleep-deprived patients. Excessive sedation is frequently seen when patients are given relatively large doses of opioids to relieve movement-related pain. Large doses of opioids have the effect of producing plasma concentrations of opioids that are too high since the patient is having minimal to no pain at rest. Strategies for managing sedation include eliminating all other (unnecessary) CNS depressant drugs, switching opioid drugs, increasing the caffeine content in the diet, and using potent psychostimulants such as dextroamphetamine or methylphenidate hydrochloride (see section Adjuvant Analgesic Drugs to Counteract Opioid-Induced Side Effects).

Unfounded fears of respiratory depression are often cited as a reason to limit opioid therapy. Respiratory depression is mediated by μ_2 opioid receptors in the brainstem, rendering the respiratory centers less responsive to the stimulatory effect of arterial carbon dioxide tension (31). Fortunately, tolerance to the respiratory depressant effect of opioids develops rapidly, and uncontrolled pain is a natural antagonist of opiate-induced respiratory depression. Respiratory depression is always associated with sedation. When a life-threatening opiate overdose is suspected, the patient should be stimulated vigorously to awaken. If this does not reverse sedation and hypoventilation, naloxone hydrochloride, an opiate antagonist, should be given intravenously. Patients on chronic opioids are more sensitive to naloxone hydrochloride than patients relatively naive to opioid administration; therefore it is recommended that a dilute naloxone hydrochloride solution should be used in this setting (14). The 0.4-mg ampule of naloxone hydrochloride can be diluted in 10 ml of normal saline and injected slowly, with titration bringing the dose to effect; this careful titration prevents the precipitation of severe withdrawal symptoms and return of pain. Naloxone hydrochloride has a half-life of only 1 hour (35) and a short duration of action; therefore, close monitoring and repeated injections might be needed in the event of a morphine sulfate overdose. Prolonged monitoring is required with opiates with a longer half-life, like methadone hydrochloride, propoxyphene, and levorphanol tartrate. It must be kept in mind that excessive drug intake is a rare cause of encephalopathy and respiratory depression in patients with cancer on a stable dosage of opiates. In fact, one study has indicated that the majority of naloxone hydrochloride administrations in a large cancer center were inappropriate (76) and could have been avoided if more care were taken to determine the true cause of sedation or if the patient were simply physically stimulated.

Other relatively uncommon opioid side effects are listed in Table 3-4. It should be noted that long-term effects of chronic opiate use on intellectual function have not been demonstrated, although acute transient cognitive effects can be seen when opioid doses are increased (77). Opioids do not mask pain from new or ongoing tissue injury, and fears of masking medical emergencies like “acute abdomen” and myocardial infarction with opioids are unfounded.

Common side effects	Uncommon side effects
Constipation	Respiratory depression
Nausea	Seizures
Sedation	Pruritus
Mental clouding	Xerostomia
	Myoclonus

TABLE 3-4. SIDE EFFECTS OF OPIOID ANALGESICS

Tolerance, Physical Dependence, and Psychological Dependence

Tolerance, which implies the need to continuously increase the dose to obtain the desired effect, is a complex and incompletely understood phenomenon. However, the overwhelming clinical experience with patients on chronic opioids indicates that when the pain is stable, tolerance to the analgesic effects of opiates does not generally develop at the rate that would be predicted by animal studies (78). When rapid escalation of the opioid dose in cancer patients is required, this almost always means that the pain stimulus has increased in relation to progressive disease associated with new or ongoing tissue injury (78). However, because tolerance to the different opioid effects develops at different rates (e.g., rapidly for respiratory depression, slower for analgesic effects, very slow if at all for constipating effects), it is usually possible to titrate the opioid doses to appropriately balance analgesia and side effects. Cross-tolerance among different opiates is incomplete, indicating that analgesia might develop when switching to a different strong opiate at an equianalgesic dose, but side effects may develop as well (78). Therefore, a 50% dose reduction of the calculated equianalgesic dose and a gradual upward titration are recommended. It has been observed that true pharmacological tolerance is seen when, in the setting of an unchanging pain stimulus, the duration of analgesia shortens (78).

Physical dependence is an altered physiologic state, produced by repeated administrations of a drug, which necessitates the continued administration of the drug to prevent the appearance of withdrawal symptoms that are characteristic for the particular drug (31). When opiates are abruptly discontinued, often in error, the withdrawal syndrome consists of lacrimation, rhinorrhea, restlessness, and tremors; these symptoms are usually mild and don't have the dramatic flavor of the withdrawal syndrome seen in the chemically dependent patient. Patients who have received repeated doses of morphine sulfate daily for 1 or 2 weeks have mild and often unrecognized withdrawal symptomatology when the drug is stopped; symptoms are delayed and even less pronounced with opioids with a long half-life like methadone hydrochloride and levorphanol tartrate. However, if an opioid antagonist is administered, symptoms of withdrawal may appear after a single dose (31). Appropriate counseling and a gradual taper of the opiate over a few days effectively prevents the development of a withdrawal syndrome. The inappropriate administration of naloxone hydrochloride may precipitate profound withdrawal in patients taking chronic opioids for pain relief.

Psychological dependence—now the preferred term for addiction—is described as compulsive drug-seeking behavior and overwhelming involvement in drug procurement and use (31). The inexperienced clinician may misinterpret the behavior of the patient with severe unrelieved pain for drug-seeking behavior because poorly managed pain may produce many of the behaviors that physicians have come to fear in “addicted” individuals. This phenomenon is recognized by the term *pseudoaddiction* (79). The rarity of psychological dependence after chronic opioid treatment has been clearly documented in several studies and reviewed in detail (80). For example, in a study involving 11,882 patients who received at least one opioid prescription, the development of addiction occurred in only four instances (81). The analysis of patterns of drug intake in patients with cancer suggests that chemical dependence does not occur in this population, or occurs only very rarely (82). An exception to this rule is offered by patients with a history of chemical dependence that antedates the cancer. Exaggerated and unfounded fears of addiction should not prevent patients from receiving opioids on a chronic basis for severe pain.

Adjuvant Analgesics in Cancer Pain Management

The adjuvant analgesics are a heterogeneous group of drugs that were marketed and approved for indications other than pain, but that may be analgesic in certain clinical conditions or counteract adverse effects of conventional opioid and nonopioid analgesics (87). As indicated in Table 3-5, adjuvant analgesics can be grouped into three broad categories: (a) general purpose drugs (e.g., tricyclic antidepressants); (b) drugs used in specific pain syndromes such as neuropathic, bone, or visceral pain (e.g., anticonvulsants for neuropathic pain, radiopharmaceuticals for bone and visceral pain); and (c) drugs used to counteract opioid analgesic side effects (e.g., caffeine, methylphenidate hydrochloride, phenothiazine antiemetics). Adjuvant analgesic drugs usually require severalweek trials to determine their usefulness and often do not provide complete analgesia. Patients should be educated as to these facts so as to make their compliance more likely.

TABLE 3-5. ADJUVANT ANALGESIC DRUGS USED TO TREAT CANCER-RELATED PAIN

General Purpose Adjuvant Analgesics

These drugs are used for a variety of pains, including those of musculoskeletal, neuropathic, and visceral origin, as well as chronic headache. The tricyclic antidepressants are the most widely used in this group. They probably produce analgesia by increasing levels of norepinephrine or serotonin in the CNS and thus may enhance the activity of endogenous pain-modulating pathways (88). Amitriptyline hydrochloride, imipramine hydrochloride, nortriptyline hydrochloride, and desipramine hydrochloride have all been demonstrated to have some analgesic efficacy (89) in chronic pain, especially pain of neuropathic origin. The doses required to produce analgesia are generally lower and the analgesic effect quicker (typical onset within 1 week) in comparison to antidepressant effects.

The selective serotonin reuptake inhibitors, although attended by fewer side effects than the tricyclic antidepressants, have a mixed picture as analgesics. For example, one randomized, controlled trial using fluoxetine hydrochloride in diabetic neuropathy could not demonstrate an analgesic effect in nondepressed patients, although at least some analgesic effect has been demonstrated for paroxetine hydrochloride in the management of painful diabetic neuropathy (90).

In general, one should start with relatively low doses of tricyclic antidepressants (especially in elderly patients) and increase the dose every 3 days. For example, a typical regimen for amitriptyline hydrochloride calls for starting at 10 mg at bedtime, increasing to 25 mg in 3 days, then increasing by 25 mg every 3–7 days until a dose of 75–150 mg is reached. Sequential trials of different tricyclics should be considered, especially selection of drugs in the secondary amine family (e.g., desipramine hydrochloride or nortriptyline hydrochloride) if the tertiary amine drugs such as amitriptyline hydrochloride are not tolerated because of adverse effects. For this reason, some clinicians prefer initiating tricyclic antidepressant therapy with desipramine hydrochloride or nortriptyline hydrochloride. The selective serotonin reuptake inhibitors are generally used as second- or third-line agents because the data supporting their efficacy in neuropathic pain are not as strong as those regarding the tricyclic antidepressant family.

Methotrimeprazine is a phenothiazine compound that has analgesic activities. Analgesic studies have confirmed that 15 mg of methotrimeprazine given intramuscularly is equipotent to 10 mg of morphine sulfate given intramuscularly (91). This drug is most useful in the setting of hospitalized patients with opioid-induced ileus because it can provide an opioid-sparing analgesic effect. The side effect profile is the same as for other phenothiazines, and orthostatic hypotension and sedation can be dose-limiting effects. Other limitations to its use are its relative expense and the fact that it is not available in an oral formulation in the United States. The parenteral formulation has been used orally by mixing in juice and drinking.

Corticosteroids may enhance analgesia in a variety of situations, including metastatic bone pain, pain related to nerve compression, and pain from epidural spinal cord compression (92). The response to corticosteroids may be rapid and dramatic. Because of the potential for serious adverse effects with prolonged use, corticosteroids are best reserved for patients with advanced disease or for short-term use.

Marijuana has attracted renewed attention as an analgesic, antiemetic, antiglaucoma agent, and appetite stimulant. When smoked, the marijuana delivers over 60 cannabinoid compounds with known or potential pharmacological activity, although the D-9 tetrahydrocannabinoid (D-9 THC) metabolite is the most pharmacologically active (93). This compound, D-9 THC, is also available as 2.5-mg dronabinol capsules. A controlled trial of dronabinol in doses of 2.5 mg twice daily (b.i.d.) compared to placebo demonstrated effectiveness in increasing appetite, improving mood, and decreasing nausea in patients with acquired immunodeficiency syndrome-related anorexia and weight loss (94).

The data regarding the efficacy of D-9 THC as an analgesic are less clear. A controlled trial comparing 10- and 20-mg oral doses to placebo and to oral doses of codeine phosphate at 30 and 60 mg in patients with cancer pain demonstrated that only the 20-mg dose could be distinguished from placebo, although dysphoria and delirium were quite prominent at this dose (95). There are no studies of the analgesic effect of smoked marijuana, although there are anecdotal reports of the use of inhaled marijuana as an analgesic (96). In summary, the existing data are unclear as to whether inhaled marijuana or D-9 THC has any advantage over existing analgesics in terms of analgesic efficacy or side effect profile.

Adjuvant Analgesic Drugs Used for Bone Pain

A more complete list of drugs useful for metastatic bone pain is given in Table 3-5. It has been shown that bisphosphonate compounds inhibit the reabsorption of bone and reduce bone pain in lytic bone metastasis, such as is typical of breast cancer (97). Table 3-5 lists the usual dosage schedule for pamidronate disodium, perhaps the most widely used bisphosphonate currently. A recent randomized, controlled trial in which pamidronate disodium was used in patients with stage IV breast cancer showed that this drug reduced further skeletal complications in this disease and significantly reduced bone pain when compared to placebo controls.

Adjuvant Analgesics Used in Neuropathic Pain

Many types of pharmacological agents have been used to manage neuropathic pain, including tricyclic antidepressants, anticonvulsants, systemic local anesthetic agents, topical anesthetic creams, capsaicin, baclofen, and clonidine. Doses of these drugs and their general indications are listed in Table 3-5. In addition, two old drugs, ketamine and dextromethorphan hydrobromide, are being reevaluated in neuropathic pain because of their ability to inhibit N-methyl-D-aspartate (NMDA) receptors, which have recently been shown to be important in neuropathic pain states (98).

Anticonvulsant drugs generally are used to manage pain refractory to conventional analgesic drugs and as first-line agents to treat lancinating pain of neuropathic origin (99). Current estimates indicate that approximately 5% of anticonvulsant drug prescriptions are written for neuropathic pain. Generally, these drugs are given in the dose ranges usually administered to treat epilepsy. Gabapentin, a g-aminobutyric acid analog, is a relatively new anticonvulsant that has received recent attention for its use in pain, particularly pain associated with neuropathic pain, sympathetically maintained pain, or other complex regional pain syndromes (100). This drug is relatively free of side effects, although drowsiness, dizzi- ness, and ataxia have been associated as dose-related effects.

Systematically administered local anesthetics may have a role in the management of neuropathic pain. Intravenous lidocaine is usually given as a 2–5 mg/kg dose over 20–30 minutes. Most clinicians do the infusion while monitoring blood pressure and heart rate in a monitored environment. Intravenous lidocaine often provides dramatic relief of neuropathic pain (101); however, the analgesic effect is usually short-lived, although it may persist well beyond the duration of the infusion (101). The efficacy of intravenous lidocaine in the management of cancer-related neuropathic pain has not been established definitively because a placebo-controlled trial could not demonstrate a difference between lidocaine and the inactive treatment (102). Mexiletine hydrochloride, an oral analog of lidocaine, may be administered to patients

in doses of 150–600 mg/day (102).

Baclofen is a g-aminobutyric acid agonist that has been used in many neuropathic pain syndromes, most notably trigeminal neuralgia, in which it is used in combination with carbamazepine when this condition is refractory to carbamazepine alone (103). There is a wide range of effective oral doses, staring at 5 mg b.i.d. up to 150 mg/day.

Epidural clonidine may be effective in selected patients with cancer pain, particularly for neuropathic pain. In one study, 85 cancer patients were titrated to pain relief on epidural morphine sulfate and then randomized to receive epidural clonidine (30 mg/hour) or placebo, with either group receiving epidural morphine sulfate rescue doses as needed. Analgesia was reestablished in 45% of the epidural clonidine group, but only 21% of the placebo group, and was more likely to occur when a neuropathic pain mechanism was the predominant pain (104). Hypotension occurred as a serious complication in only two patients on epidural clonidine.

As already mentioned, activation of the NMDA receptor by endogenous ligands, such as the excitatory amino acids, glutamate, and aspartate, promotes pain and hyperalgesia after experimental peripheral nerve injury, and blockade of this receptor by drugs such as dextromethorphan hydrobromide relieves pain (105). Ketamine and dextromethorphan hydrobromide are competitive NMDA receptor antagonists and produce analgesia in neuropathic pain (98). Ketamine blocks NMDA receptors and produces analgesia in doses much lower than those needed to produce anesthesia, and is typically given by continuous infusion at 0.1–1.5 mg/kg/hour. The infusion can be repeated as needed. Dextromethorphan hydrobromide is an antitussive and is present in many cough syrup formulations. It also can be given as a single entity in a slow-release preparation known as Delsym, in doses ranging from 15 mg to 500 mg b.i.d. Better controlled trials of these agents are required to determine the ultimate usefulness of ketamine and dextromethorphan hydrobromide as NMDA receptor blockers in neuropathic pain. Side effects common to these agents include sedation (ketamine and dextromethorphan hydrobromide) and delirium (ketamine).

Adjuvant Analgesics Used for Visceral Pain

Several drugs useful for visceral pain are listed in Table 3-5. Octreotide acetate, a synthetic analog of somatostatin, can be given intrathecally to produce analgesia but has also been administered as a subcutaneous infusion to manage nausea, vomiting, and diarrhea associated with malignant bowel obstruction (106).

Adjuvant Analgesic Drugs to Counteract

Opioid-Induced Side Effects Psychostimulants such as caffeine (107), methylphenidate hydrochloride, pemoline, and dextroamphetamine also have a place in cancer pain treatment (Table 3-5). Methylphenidate hydrochloride has been shown to enhance the analgesic effect of opioid drugs and to decrease the sedation associated with opioid use (108).

SUMMARY

Currently available pain management techniques make adequate pain control a realistic and achievable goal for virtually all patients with cancer. A thorough evaluation of the pain complaint to establish a pain diagnosis is the key to successful management. Special attention should be paid to those pain syndromes potentially responsive to primary antineoplastic treatment so that such treatment can be initiated in a timely manner when appropriate.

Individualized pharmacotherapy is the cornerstone of cancer pain management, and usually requires the use of opioid analgesics, often in combination with nonopioid analgesics and adjuvant medications. Opioids should be administered on a scheduled basis with the dose titrated to achieve a balance between pain control and adverse side effects. The risk of addiction in the cancer patient with pain is negligible and should not discourage the appropriate use of this highly effective class of analgesics.

In a minority of patients, cancer pain cannot be adequately controlled by systematically administered analgesics, often because of intractable dose-limiting side effects. For these patients, interventional approaches should be considered, including either anesthetic or neurosurgical procedures. Appropriate patient selection is critical to maximizing the success of these procedures. Optimal pain management in the patient with cancer requires individualization of treatment and the integration of pain management approaches.

Many factors affect the pain experience, including physical, psychosocial, and emotional influences. Conversely, uncontrolled pain may have a disastrous impact on all aspects of patient function and quality of life. Adequate pain management, ideally in a multidisciplinary setting, should therefore be viewed as a high priority for all patients with cancer.

CHAPTER REFERENCES

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4

NONOPIOID AND ADJUVANT ANALGESICS

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Analgesic drugs can be divided into three categories: opioid, nonopioid, and adjuvant analgesics. The term nonopioid analgesic is conventionally applied to acetaminophen (paracetamol), all of the nonsteroidal anti-inflammatory drugs (NSAIDs), and several other compounds, such as dipyrone. The term *adjuvant analgesic* refers to any drug that has a primary indication other than pain, but is known to be analgesic in specific circumstances.

NONOPIOID ANALGESICS

The NSAIDs constitute a very diverse group of drugs (Table 4-1), all of which inhibit the enzyme cyclooxygenase and thereby reduce the synthesis of prostaglandins. As recommended in the “analgesic ladder” approach to the management of cancer pain (1), these drugs may be used alone for mild to moderate pain, or may be combined with opioid and adjuvant analgesics during the treatment of more severe pain.

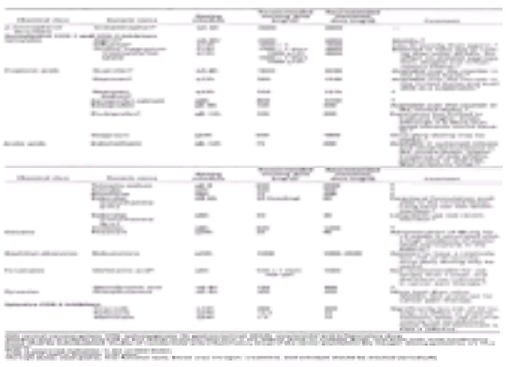

TABLE 4-1. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Clinical Pharmacology of Nonsteroidal Anti-Inflammatory Drugs

Cyclooxygenase has two isoforms: the constitutive variety known as *cyclooxygenase-1* (COX-1) and an inducible variety known as *cyclooxygenase-2* (COX-2)(2,3). COX-1 is involved in the normal physiology of the stomach, kidney, platelets, and, presumably, other organs and tissues as well. Although COX-2 appears to be constitutive in limited tissues (e.g., brain and kidney), it is largely produced in response to injury and, as such, is a key element in the inflammatory cascade.

As a result of this pharmacology, it has been recognized for some time that preferential inhibition of COX-2 might lead to a relatively improved toxicity profile without loss of anti-inflammatory or analgesic effects (4). As expected, studies of selective COX-2 inhibitors have provided strong evidence of a relatively reduced risk of gastrointestinal toxicity and no effect on platelet function (5,6). There is, however, no evidence of improved renal toxicity from these drugs.

At the present time, the selective COX-2 inhibitors include celecoxib, rofecoxib, valdecoxib, and meloxicam (at lower doses). Other compounds are in development and are likely to enter the marketplace. All other NSAIDs are nonselective inhibitors of both COX-1 and COX-2. There are, however, very large differences in the degree to which these drugs inhibit the two isoforms, and to some extent, these differences may account for the variation in risk of gastrointestinal toxicity identified in epidemiological surveys (7).

All NSAIDs are both analgesic and anti-inflammatory. In contrast to acetaminophen (paracetamol), the mechanism of which presumably involves inhibition of COX in the central nervous system, NSAIDs inhibit both central and peripheral COX (8). The central effects of the NSAIDs presumably account for some of the observed disparity between the anti-inflammatory and analgesic potencies of some of the drugs in this class (9).

The NSAIDs produce dosedependent analgesic effects, and have dose–response relationships characterized by a minimal effective dose and a ceiling dose for analgesia. Doses higher than the ceiling do not provide additional analgesia, but appear to increase the risk of toxicity. There is large individual variation in the minimal effective dose, toxic dose, ceiling dose, and the recommended therapeutic doses for each drug. Because the recommended doses have been extrapolated from dose-ranging studies in relatively healthy populations, they should be viewed as broad guidelines rather than as absolute requirements, particularly in the medically ill and the elderly. To enhance the safety of long-term NSAID therapy, dose escalation from a relatively low initial dose is appropriate.

There is great variability in response to NSAIDs. Although there are few empirical data, clinical observations suggest that these drugs have relatively better efficacy in pain related to bone injury and inflammatory processes, and relatively poorer efficacy in neuropathic pain. Notwithstanding, there is no evidence that some types of pain are wholly unresponsive to these drugs.

There is also large intraindividual variability in the response to the different NSAIDs. Although the reason for this is not understood, it suggests the potential utility of sequential trials in those who do not respond initially to treatment.

NSAIDs have well-defined toxicities. The most important risk of the nonselective COX inhibitors is gastroduodenopathy, which affects approximately 10% of patients treated overall; ulcers occur in approximately 2% (10). As noted, this risk is substantially reduced, but not eliminated, during treatment with the COX-2 selective drugs (4–6). Nausea and abdominal pain are poor predictors of serious NSAID-related toxicity. As many as two-thirds of patients being treated with NSAIDS experience no symptoms before hemorrhage or perforation. Among the factors that have been associated with an increased risk of ulceration are advanced age, the use of higher NSAID doses, concomitant administration of a corticosteroid, and a history of either ulcer disease or previous gastrointestinal complications from NSAIDs (10,11). Heavy alcohol or cigarette consumption may also increase risk. The bacterium *Helicobacter pylori* also has been implicated as a factor in NSAID-related gastropathy

(12).

The risk of NSAID-induced ulcer disease can be reduced by coadministration of other drugs (13). For example, misoprostol, a prostaglandin analog, reduces the incidence of NSAID-induced gastric ulcers without reversing anti-inflammatory and analgesic effects (14). The cost of long-term therapy, as well as its tendency to produce diarrhea and abdominal bloating, limit the use of this drug. Several studies have confirmed that coadministration of a proton pump inhibitor, such as omeprazole, can reduce the risk of NSAID-induced gastric and duodenal ulcers (15), and although studies of H_2 blockers have not been uniformly favorable, there is evidence that these drugs can also be beneficial. One such study indicates that higher-dose (40 mg per day), but not lower-dose, famotidine is effective (16), suggesting that the dose of these drugs may need to be relatively high to reduce the risk of NSAID-induced ulcer formation.

Other agents, such as antacids and sucralfate, have never been shown to reduce NSAID risk. These therapies can be used to blunt disturbing symptoms, such as pyrosis, but should not be coadministered for ulcer prophylaxis unless patients are not candidates for therapy with misoprostol, a proton pump inhibitor, or an H_2 inhibitor.

Acetaminophen (paracetamol) and the NSAIDs, including the selective COX-2 inhibitors, can cause serious renal toxicity. These drugs must therefore be used cautiously in patients who have clinically evident renal disease, or who are likely to have subclinical disease as a result of advanced age, prior nephrotoxic therapy (e.g., platinum-based chemotherapy), or underlying disease (e.g., diabetes or sickle cell disease) known to place the microcirculation at risk of compromise. NSAIDs also are associated with fluid overload, which may occur in the absence of renal insufficiency and contribute to edema or other major complications such as congestive heart failure (17).

NSAID-induced inhibition of platelet aggregation may cause a clinically significant bleeding diathesis. A single dose of aspirin irreversibly alters exposed platelets and can double the bleeding time for up to 1 week. The effect of other NSAIDs on platelet function is reversible, and these drugs prolong bleeding time only when circulating in the plasma. Acetaminophen and the selective COX-2 inhibitors do not affect bleeding time. The nonacetylated salicylates, such as choline magnesium trisalicylate and salsalate, are believed to have minimal platelet effects and also presumably pose less risk.

A secondary analysis of a controlled trial of rofecoxib raised concern about excess risk of cardiovascular events associated with selective COX-2 inhibition (18). However, a combined analysis of controlled trials has not confirmed this risk (19), and suggests instead that the difference in cardiac events between those treated with the COX-2 selective and the nonselective COX inhibitors is more likely due to a relatively reduced risk among the latter group.

Patients occasionally develop dizziness, confusion, or headache during NSAID therapy. Headache appears to be relatively more frequent during treatment with indomethacin than with other NSAIDs. Dizziness and confusion appear to be more common in the elderly, and patients rarely develop a delirium after NSAID treatment.

Nonsteroidal Anti-Inflammatory Drug Administration

In the medically frail, the need to avoid a gastrointestinal complication may be sufficient to justify the first-line use of a relatively selective COX-2 inhibitor, such as celecoxib, rofecoxib, or meloxicam. If the costs of these drugs are prohibitive or they are unavailable, the use of a relatively safe nonselective NSAID, perhaps combined with a gastroprotective drug, may be appropriate. Although pharmacoeconomic modeling suggests that COX-2 selective drugs may be relatively cost beneficial, particularly in the medically ill (19), further empirical studies are needed to confirm this. Indeed, there have been no clinical trials of the COX-2 selective inhibitors in the medically ill, and the degree to which the use of these drugs improves outcomes remains speculative.

Regardless of the drug selected, it is prudent in those with serious medical illness to consider initiating NSAID therapy at a relatively low dose and then to gradually increase the dose based on response. In patients who are less frail, conventional starting doses can be used as initial therapy. Those with acute, relatively severe pain should be considered for an initial loading dose of 1–2 times the conventional starting dose.

If dose titration is attempted, patients must be carefully monitored between dose changes. Although several weeks may be needed to produce maximal effects, the likelihood of benefit from a dose change can usually be judged within 1–2 weeks. The occurrence of increased analgesia after a dose change suggests that the patient is below the ceiling dose for the drug. If analgesia is not adequate in this setting, the dose can be increased further unless side effects occur or the dose has reached the conventionally accepted maximum. This maximum dose is usually 1–2 times the recommended starting dose. If a dose increment does not yield greater analgesia, the ceiling dose presumably has been reached and further dose increases are not justified. If a satisfactory balance between analgesia and side effects cannot be attained at a dose below the maximal safe dose, the drug should be discontinued, and an alternative NSAID should be considered.

Long-term NSAID therapy usually should be accompanied by regular monitoring for common adverse effects. This may include screening for occult fecal blood and tracking hemoglobin, renal function, and hepatic function. Patients who are predisposed to adverse effects and those who are receiving relatively high doses should be monitored every few months; others may be monitored less frequently.

ADJUVANT ANALGESICS

The term “adjuvant analgesic” can apply to numerous drugs in a variety of classes (Table 4-2) (20). In populations with serious medical illness, these medications usually are considered after opioid therapy has been optimized. This conventional practice derives from the observation that opioid drugs generally are more reliable and have a more predictable side effect profile. Although first-line use of an adjuvant analgesic sometimes is pursued when patients have a marked predisposition to opioid toxicity, or a type of pain that experience suggests may be relatively more responsive to the adjuvant (e.g., first-line treatment of lancinating neuralgias with an anticonvulsant), these occurrences are relatively uncommon in the medically ill. Typically, the adjuvant analgesics are administered to those patients whose pain has responded poorly to optimal opioid therapy.

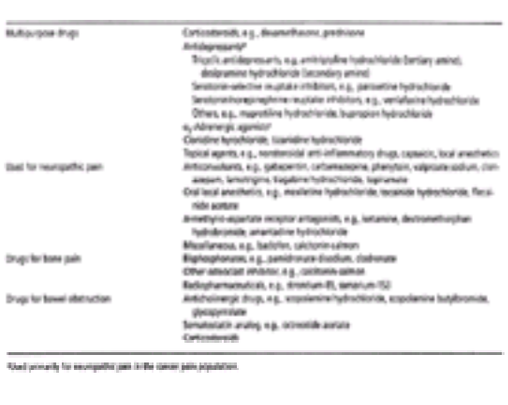

TABLE 4-2. ADJUVANT ANALGESICS

To administer an adjuvant analgesic appropriately, the clinician should be familiar with the approved indications, unapproved indications accepted in medical practice, likely side effects, potential serious adverse reactions, usual time–action relationship, pharmacokinetics, and specific dosing guidelines for pain. Very few of the adjuvant analgesics have been studied in the medically ill, and the information used to develop dosing guidelines usually is extrapolated from other patient populations. The existence of large inter-individual and intraindividual variability in the response to all adjuvant analgesics suggests that sequential therapeutic trials often are needed to identify the most useful drug. A patient's response to other drugs, including those in the same class, does not reliably predict the outcome of a therapeutic trial.

Some classes of adjuvant analgesics have been studied in a variety of pain syndromes and are best considered multipurpose analgesics. These include the corticosteroids, the antidepressants, the a_2-adrenergic agonists, and a variety of topical therapies. With the exception of the corticosteroids, however, this designation as multipurpose analgesics has limited resonance in the medically ill because of the widespread use of opioid therapy. Although the antidepressants, the a_2-adrenergic agonists, and topical therapies potentially could be used for all types of pain, they are typically administered to those who have not responded adequately to opioid therapy. Of the latter group, patients with refractory neuropathic pain usually are the targets for therapeutic trials with these agents.

CORTICOSTEROIDS

In the cancer population, corticosteroids have been shown to improve pain and appetite, diminish nausea and malaise, and increase patients' overall quality of life (21,22 and 23). They are commonly used to treat refractory neuropathic pain, bone pain, pain associated with capsular expansion or duct obstruction, pain from ascites or bowel obstruction, pain caused by lymphedema, and headache caused by increased intracranial pressure (21,23,24,25 and 27). Although the data suggest a relatively high likelihood of favorable outcomes during treatment with these drugs, most studies are uncontrolled, and there has been no evaluation of drug-selective differences, dose–response relationships, predictors of efficacy, or the durability of favorable effects.

The analgesic effects of corticosteroids likely result from a variety of mechanisms. They are anti-inflammatory and may reduce mass effect caused by edema or inhibit the release of inflammatory mediators that sensitize or activate primary afferent nerves. They also may have direct actions on injured neurons (28). If positive mood effects occur, these may augment analgesic effects, as well as increase a sense of well-being.

The risk of adverse effects associated with corticosteroid therapy increases with both the dose and duration of therapy. Long-term administration is usually considered only for patients with advanced disease whose limited life expectancy and overriding need for symptom control justify the risk. In this context, surveys of low-dose corticosteroid therapy indicate that the risk of serious adverse effects is low (24,26). The most common adverse effects are oral candidiasis and myopathy. Potential serious adverse effects include increased risk of infection, diabetes, fluid overload (ranging from peripheral edema to congestive heart failure), cushingoid habitus, increased risk of skin breakdown, and neuropsychiatric syndromes (ranging from mild dysphoria or mental clouding to severe anxiety, depression, or even psychosis).

Most corticosteroid therapy involves long-term administration of relatively low doses. This may involve treatment with prednisone (5–10 mg) or dexamethasone (1–2 mg) once or twice daily. Treatment is continued as long as potential benefits appear to outweigh adverse effects. Dose escalation for worsening symptoms is appropriate if benefits decline with progressive disease, particularly at the end of life.

Another approach to corticosteroid therapy is appropriate for selected patients with severe pain. The usual setting is characterized by rapidly worsening pain related to nerve injury, bony lesion, or duct obstruction that has failed to respond promptly to an opioid. The regimen often begins with dexamethasone, 100 mg intravenously, followed by 96 mg daily in four divided doses. The dose is gradually tapered over weeks as an alternative analgesic approach is implemented, such as radiation therapy or neural blockade.

ADJUVANT ANALGESICS USED FOR NEUROPATHIC PAIN

Many adjuvant analgesics are primarily used in medically ill populations for the treatment of neuropathic pain that has not responded adequately to opioid therapy. Drug selection usually reflects the clinician's best judgment about the risks associated with the therapy, the likelihood of analgesia, and the possibility of secondary beneficial effects on symptoms other than pain.

Neuropathic pain is perhaps the most common target of adjuvant analgesic therapy. At the present time, gabapentin is the most common adjuvant analgesic used for neuropathic pain. This drug is an anticonvulsant with an obscure primary mechanism of action and proven efficacy in different neuropathic pain syndromes (29,30 and 31). Favorable effects and good tolerability have been demonstrated in a series of patients with cancer-related neuropathic pain (32). It has an acceptable adverse effect profile, is not metabolized in the liver, and has no known drug-drug interactions. Treatment usually starts with 100–300 mg per day, and dose titration usually continues until benefit occurs, side effects supervene, or the total daily dose is at least 3600 mg per day. The rate of titration is usually determined by the severity of the pain and the development of side effects. Dose increments can occur daily or every other day, or be instituted much more gradually. The dose at which response occurs is highly variable. Some patients respond favorably (or conversely, develop treatment-limiting side effects) at 600 mg per day in divided doses, whereas others do not reach a maximal response until the dose is increased to 6000 mg per day or higher.

Numerous other drugs may be effective for neuropathic pain. Patients who have not responded well to gabapentin, or lack access to this drug, are usually offered an antidepressant, an alternative anticonvulsant, or a corticosteroid. Other drug classes are tried in refractory cases.

Antidepressants

The analgesic efficacy of antidepressant medications has been well established (31,33). This analgesia is believed to result from their actions on endogenous monoaminergic pain-modulating systems, particularly those that use norepinephrine or serotonin. Although the positive mood effects of these agents may be beneficial, they are not required for analgesic efficacy. As noted, the broad range of pain syndromes that may respond and the analgesic response of patients without mood disorders suggest that these drugs could be categorized as multipurpose analgesics. Unfortunately, there are almost no controlled trials in populations with serious medical illness.

There is an extensive body of evidence-based data supporting the analgesic efficacy of the tricyclic antidepressants (TCAs) (31,33,34,35,36 and 37). Both the tertiary amine TCAs, such as amitriptyline hydrochloride, doxepin hydrochloride, imipramine hydrochloride, and clomipramine hydrochloride, and the secondary amine compounds, such as desipramine hydrochloride and nortriptyline hydrochloride, are analgesic. The evidence is strongest for amitriptyline hydrochloride.

In contrast to the TCAs, there are very few controlled trials of the selective serotonin reuptake inhibitors (SSRIs) or the selective serotonin and norepinephrine reuptake inhibitors. There are also few trials of other nontricyclic compounds, such as maprotiline hydrochloride or bupropion hydrochloride. There is evidence to support the analgesic effects of some of these drugs, such as the SSRI paroxetine hydrochloride (38), maprotiline hydrochloride (39), and bupropion hydrochloride (40). Anecdotal reports of some of the others, such as venlafaxine hydrochloride, also have been favorable. There are very few comparative trials of the antidepressants. Those extant have generally indicated that the tertiary tricyclic drugs are the most likely to yield analgesia (36).

The available evidence suggests that the antidepressant drugs can relieve both continuous and paroxysmal neuropathic pains (35,36). Extensive clinical experience supports greater utility in continuous pain. At this time, therefore, the usual practice is to consider other categories of adjuvant analgesics first for lancinating or paroxysmal neuropathic pains (see the section Anticonvulsants and Related Drugs)

On the basis of the available evidence, it is reasonable to select a TCA first if pain is the target symptom. As noted, amitriptyline is the best studied TCA, but the anticholinergic, sedative, or hypotensive effects of this drug may relatively contraindicate it in the medically ill. If so, a trial with a secondary amine TCA, desipramine hydrochloride or nortriptyline hydrochloride, is appropriate given the better side effect profile of this class. If the tricyclics are not tolerated, a trial of an SSRI (e.g., paroxetine hydrochloride) or one of the other established analgesics should be considered.

It is prudent to initiate antidepressant therapy at relatively low doses, regardless of the drug class. The TCAs are most safely begun at 10–25 mg at night. The dose should be increased every few days by the size of the starting dose. Studies of the TCAs indicate that analgesic effects usually occur within 4 to 7 days after achieving an effective daily dose, which is typically in the range of 50–150 mg for amitriptyline hydrochloride and desipramine hydrochloride. Doses should be increased further if neither analgesia nor intolerable side effects occur, or if pain is complicated by depression.

Although there are no data correlating specific plasma drug concentrations with effective analgesia, measurement of TCA plasma drug concentration can be a useful therapeutic guide. If adherence to therapy is good, a relatively low concentration (compared to the reference antidepressant range) suggests poor absorption or rapid metabolism of the drug. In the absence of side effects, such a finding warrants dose escalation regardless of the administered dose. Conversely, dose escalation usually is not attempted if the plasma concentration equals or exceeds the upper limit of the range for antidepressant efficacy. Monitoring of the TCAs with an electrocardiogram is also prudent as higher doses are reached, given the association between these drugs and atrioventricular conduction disorders.

An antidepressant should be discontinued if unsatisfactory side effects occur despite appropriate dose escalation. After a few weeks of treatment, it is prudent to taper the dose gradually before treatment is terminated to reduce the risk of withdrawal phenomena, such as insomnia or mood change.

Similar to antidepressant effects, the analgesic effects produced by the different antidepressant drugs can vary remarkably in the individual patient. This observation is true even among drugs in the same subclass, such as the tertiary tricyclic compounds. As a result, the failure of one antidepressant drug does not portend the failure of others, and patients should be considered for other antidepressant trials if treatment is not beneficial.

Anticonvulsants and Related Drugs

Numerous anticonvulsant drugs other than gabapentin have been evaluated as treatments for neuropathic pain (31,41,42). Based on several decades of clinical experience, the commercial success of gabapentin, and a slowly growing evidence base, these drugs are now often considered first for neuropathic pain that is

paroxysmal or lancinating in quality, and, along with the antidepressants, are among the first-line treatments for neuropathic pains of other types.

Many of the older anticonvulsant drugs have longstanding use in pain management. These include carbamazepine, phenytoin, divalproex sodium, and clonazepam (41,42). Clinical experience is most extensive with carbamazepine, but this drug's utility may be lessened by its potential to produce bone marrow suppression, particularly leukopenia. Phenytoin and divalproex sodium can be initiated with loading doses, which may be favorable in the setting of very severe pain. Clonazepam, a benzodiazepine, has anxiolytic and hypnotic effects that may address other problems in the medically ill.

All of the newer anticonvulsants, including lamotrigine, topiramate, tiagabine hydrochloride, oxcarbazepine, pregabalin, zonisamide, and levetiracetam, are used empirically in the treatment of refractory neuropathic pain. The evidence of analgesic efficacy is strongest for lamotrigine (43). However, this drug requires a relatively slow initial dose titration period to reduce the likelihood of cutaneous hypersensitivity, which may limit its utility among those with advanced illness. A trial of felbamate should be considered only in extreme cases because of its potential for life-threatening aplastic anemia.

All anticonvulsants are administered using the dosing schedules typically employed for seizures. Plasma concentrations of carbamazepine, phenytoin, and valproate sodium can be monitored to ensure that maximum anticonvulsant doses have been reached if pain relief does not occur with routine dose escalation.

Like other adjuvant analgesics, anticonvulsant agents are characterized by large interindividual and intraindividual variability in analgesic responses. Sequential trials may be necessary to identify the most useful agent.

Several nonanticonvulsants also have been evaluated in patients with paroxysmal neuropathic pain, and historically have been considered together with the anticonvulsants for this reason. Both the gamma-aminobutyric acid agonist baclofen (44) and the neuroleptic pimozide (45) have been shown to be effective in treating trigeminal neuralgia. Whereas the side effect profile of pimozide has limited its applications, baclofen has attained widespread acceptance as a useful drug for all types of neuropathic pain. It has not been studied in syndromes other than trigeminal neuralgia, however, and has not been specifically evaluated in populations with serious illness. Nonetheless, the favorable anecdotal experience suggests that a trial may be considered for patients with any type of neuropathic pain. The therapeutic dose appears to vary widely, ranging from 30 mg to more than 200 mg/d. Gradual dose escalation from a low initial dose reduces the risk of side effects. Serious withdrawal phenomena can occur after abrupt discontinuation of this drug, and tapering of the dose is necessary if treatment has been in place for more than a few days.

Oral Local Anesthetics

Systemic administration of local anesthetics may produce analgesia in a variety of pain syndromes, including neuropathic pain. In controlled clinical trials, these drugs have been shown to be effective in treating both continuous and paroxysmal pains (46,47). Brief intravenous local anesthetic infusions also are analgesic (48).

There is limited experience in the use of these drugs for neuropathic pain in the medically ill (49). Accordingly, they are generally considered second-line analgesic agents for neuropathic pains that have not responded to one or more trials of the anticonvulsant and antidepressant analgesics.

In the United States, mexiletine hydrochloride has been the most frequently used oral local anesthetic for the treatment of pain. This preference is not based on comparative trials with other local anesthetics, such as tocainide hydrochloride or flecainide acetate. The latter drugs are also used for this indication, and regional preferences based on anecdotal experience appear to determine the drug selected. Mexiletine hydrochloride may have a relatively wider therapeutic index and the decreased incidence of cardiac and neurological toxicity, and this may justify its use in the medically ill.

All the local anesthetics are sodium channel blockers and can cause clinically significant cardiac dysrhythmias. These drugs should be used cautiously in patients with cardiac disease (previous myocardial infarction, symptomatic coronary artery disease, or dysrhythmia), and the electrocardiogram should be monitored as doses are increased.

Although the mexiletine hydrochloride plasma concentration–response relationship has not been defined in terms of analgesia, measurement of the plasma level can be informative in a manner similar to drug concentration monitoring during a TCA trial. Gastrointestinal toxicity (usually nausea) and central nervous system side effects (usually dizziness) often are dose limiting, and may require a change to an alternative therapy.

Brief intravenous local anesthetic infusion can produce pain relief that outlasts the period of measurable drug concentration by a prolonged period. Some patients who have not been responsive to oral therapy appear to respond to infusions, although this is anecdotal. More important, an intravenous local anesthetic infusion may be a useful approach to rapidly manage severe, opioid-unresponsive neuropathic pain. Although there are very limited data suggesting that the response to a brief infusion predicts the effects of oral local anesthetic therapy (50), the use of infusion to guide decisions about oral therapy is not yet justified.

The largest clinical experience with local anesthetic infusions involves lidocaine. This drug is usually administered at a dose range of 2–5 mg/kg over 20–30 minutes. This dose range has not been systematically evaluated in the medically ill, and safety considerations warrant a relatively low initial dose. Given empirical data that indicate dose-dependent effects and a possible “threshold” dose (51,52), the decision to initiate therapy with a modest lidocaine dose should be accompanied by a willingness to repeat the infusion one or more times at progressively higher doses, if neither beneficial effects nor side effects occur.

Topical Therapies

Topical analgesic therapies can benefit medically ill patients with chronic pain by providing pain relief that complements a systemic analgesic regimen with limited risk of additional systemic side effects. The role of topical therapies in pain management is evolving as clinical trials and anecdotal experience expands (53).

Topical local anesthetics have been used empirically for all types of neuropathic pain. Additionally, these formulations may have a role to play in the treatment of pains sustained by injury to skin or subcutaneous tissues.

Cutaneous anesthesia can be produced by topical application of local anesthetics, such as EMLA (*e*utectic *m*ixture of *l*ocal *a*nesthetics) (54) or high-concentration lidocaine (55). EMLA is the only commercially available topical local anesthetic formulation that can produce dense cutaneous anesthesia. Although this phenomenon may offer a theoretical advantage, cutaneous anesthesia may not be needed to yield analgesic effects in patients with neuropathic pain, and alternative local anesthetic creams or gels may be useful.

A lidocaine-impregnated patch has been developed and is approved in the United States for the treatment of postherpetic neuralgia (56). This formulation has been well accepted by patients and is now used for all types of neuropathic pain (57).

Comparative trials of the various topical local anesthetics have not been performed. Given the cost of EMLA, it is reasonable to consider a trial of this formulation after an initial trial of the lidocaine patch or a 5% lidocaine cream. The patch has been approved with instructions to apply it 12 hours per day. Anecdotal experience suggests that some patients have a better outcome with 24-hour administration. The dosing method and frequency for creams and gels are empiric. If simple application is not effective, an effort should be made to apply these formulations under an occlusive dressing.

There is substantial evidence that topical NSAIDs can be effective for soft tissue pain and perhaps joint pain (58). A trial of a formulation containing diclofenac, ketoprofen, or another NSAID is reasonable when pain is related to chronic soft tissue injury. Although there is no evidence that these formulations are useful for neuropathic pain, an NSAID is sometimes added to a compounded multidrug formulation for refractory cases, based on anecdotal experience.

Patients with neuropathic pain resulting from peripheral nerve injury can also be considered for a trial of topical capsaicin, a compound that depletes peptides in small primary afferent neurons, including those that mediate nociceptive transmission (e.g., substance P). Although efficacy in treating neuropathic pain has been suggested in both open-label and controlled studies (59,60 and 61), clinical experience has been mixed. A therapeutic trial of the high-concentration formulation (0.075%) is reasonable in patients with neuropathic pain presumed to have a strong peripheral input. An adequate trial is generally believed to require three to four applications daily for 3–4 weeks. Some patients experience burning, which may disappear over time or remit with the use of an oral analgesic, cutaneous application of lidocaine 5% ointment, or use of the lowerconcentration formulation (0.05%).

There is limited evidence that topical capsaicin may be effective for painful arthropathy affecting small joints (62). An empirical trial for this type of pain may be implemented like those for neuropathic pain. Capsaicin dissolved in a lozenge also has been suggested as a novel approach to pain related to mucositis (63). This observation has yet to be confirmed.

Other drugs are now being used topically, most with limited proof of efficacy. A trial of a TCA, such as doxepin hydrochloride, gains support from a controlled clinical trial in neuropathic pain (64). There are favorable anecdotal reports of topical opioids for pain associated with a variety of lesions (65,66). The effectiveness of this

approach remains to be confirmed. A variety of other drugs have been compounded and tried empirically as topical therapy, including ketamine and gabapentin. There have been limited favorable anecdotal observations, and further studies of these approaches are needed.

a_2-Adrenergic Agonists

The a_2-adrenergic agonists, including clonidine hydrochloride and tizanidine hydrochloride, have established analgesic efficacy in a variety of pain syndromes (67,68). Like the antidepressants, these drugs are nonspecific analgesics typically used as adjuvant analgesics for neuropathic pain in populations with serious medical illness.

The efficacy of clonidine hydrochloride in neuropathic pain has been suggested by controlled trials of transdermally administered drug in patients with painful diabetic neuropathy (67) and a controlled study of epidurally administered clonidine hydrochloride in cancer pain (69). The transdermal trial demonstrated that only approximately one-fourth of patients report any significant analgesic effect. The epidural trial revealed relatively better efficacy for neuropathic pain than pain of other types. Although tizanidine hydrochloride relieves experimental neuropathic pain in animal models (70), and anecdotal experience has been favorable, there have been no controlled trials in clinical neuropathic pain.

A systemic trial of an a_2-adrenergic agonist for neuropathic pain is usually considered after trials of other adjuvant analgesics have failed. There have been no comparative trials, and drug selection is empirical. The most common side effects of the a_2-adrenergic agonists are somnolence and xerostomia, and the most serious risk is hypotension. Tizanidine hydrochloride may be less likely to produce a change in blood pressure, and for this reason, may be preferred in populations with serious medical illness. Regardless of the drug, treatment typically begins with a very low dose, which is followed by gradual dose escalation until analgesia occurs or treatmentlimiting toxicity supervenes.

N-Methyl-D-Aspartate-Receptor Antagonists

Preclinical studies during the last decade have established that binding of the excitatory amino acid glutamate at various subunits of the N-methyl-D-aspartate (NMDA) receptor is involved in the mechanisms that may underlie some neuropathic pains and the mechanisms involved with the development of opioid tolerance (71,72). On the basis of these findings, NMDA-receptor antagonists have undergone intensive investigation as potential analgesics. Results have been mixed, but the hope remains that drugs that interact with this receptor will become useful in the treatment of refractory pain.

Three NMDA antagonists are commercially available in the United States: the dissociative anesthetic ketamine, the antitussive dextromethorphan hydrobromide, and the antiviral amantadine hydrochloride. Intravenous and oral ketamine has been shown to be analgesic in both controlled trials and case reports (73,74,74,75,76 and 77). The side effect profile of this drug, which includes mental clouding, mood changes, nightmares, and delirium, is troublesome, and its relatively narrow therapeutic window suggests that future use is likely to be limited. It has been administered in cases of severe refractory pain, either as an infusion at subanesthetic doses or orally. The infusion typically is initiated at a dose as low as 0.1–1.5 mg/kg/h, then gradually increased. Coadministration of a benzodiazepine or neuroleptic may be used to reduce the likelihood of adverse effects.

In a controlled trial, dextromethorphan hydrobromide was analgesic for the pain of diabetic neuropathy but not postherpetic neuralgia (78). This effect was associated with a relatively high mean dose of approximately 350 mg/d. Other controlled studies suggest that a 1:1 combination of dextromethorphan hydrobromide and morphine sulfate increases the analgesic effects produced by the morphine sulfate alone (79). The difference in potency suggested in these studies may relate to the effect of tolerance reversal in contributing to the analgesia produced when the drug is added to an opioid regimen. Although these studies together suggest that dextromethorphan hydrobromide may be a useful analgesic or coanalgesic, clinical experience continues to be very limited, and the utility of the drug in practice remains ill defined. A trial of dextromethorphan hydrobromide may be initiated using a commercially available antitussive that contains neither alcohol nor guaifenesin. The starting dose, which can be as high as 120–240 mg/d in three to four divided doses, can be increased gradually. Doses higher than 1 g have been administered safely, at least for the short term.

A single dose controlled trial of amantadine hydrochloride demonstrated that this drug can have analgesic effects in cancer-related neuropathic pain (80). Additional experience with chronic administration is needed to determine whether the drug can play a role in medically ill patients with opioid-refractory pain.

Magnesium also interacts with the NMDA receptor. Increased local concentration of this ion inhibits the receptor in a manner similar to competitive antagonists (81). There have been some anecdotal observations suggesting that magnesium infusion may be useful in chronic opioid unresponsive neuropathic pain (82). Further evaluation of this observation is warranted.

Neuroleptics

As described previously, pimozide may be analgesic in patients with lancinating or paroxysmal pains (45). Other neuroleptics, such as fluphenazine and haloperidol, have been administered for other types of neuropathic pain. The supporting data are very meager, however, and given the potential for side effects, the use of these drugs is best limited to the treatment of delirium. Although methotrimeprazine, a phenothiazine neuroleptic, has established analgesic effects and did at one time play a role in analgesic management at the end of life, it is no longer commercially available in the United States. There is no evidence at this time that any of the newer atypical neuroleptics have analgesic effects.

Benzodiazepines

The anticonvulsant clonazepam often is used to treat paroxysmal neuropathic pains. Although a survey of patients with mixed types of cancer-related neuropathic pains suggested that alprazolam also may have analgesic effects (83), the use of this drug is still focused on the management of anxiety. Patients with pain commonly experience both anxiety and muscle spasms, phenomena that may exacerbate the intensity of pain and respond well to benzodiazepines, such as diazepam. It may be useful, therefore, to try a benzodiazepine if these comorbidities are noted, even if the primary goal of treatment is pain control.

Calcitonin-Salmon

Two controlled trials, one in patients with reflex sympathetic dystrophy (84) and the other in patients with acute phantom pain (85), have suggested that calcitoninsalmon may be effective in neuropathic pain. Its mechanism of action in these conditions is not understood, and additional trials are needed to confirm benefit. Nonetheless, the favorable side effect profile of this drug and the convenience of the available intranasal formulation may justify a therapeutic trial in patients with refractory neuropathic pain. The usual starting dose is 200 IU/d, which may be increased several times to clarify the pain response.

DRUGS FOR COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (type I, also known as *reflex sympathetic dystrophy*, and type II, also known as *causalgia*) is a subtype of neuropathic pain characterized by regional pain, swelling, and other signs of autonomic dysregulation (86). A clinical diagnosis, it is presumably a set of disorders that ultimately will be distinguished by variation in pathophysiology. An important subtype is sustained by sympathetic efferent function (so-called sympathetically maintained pain), and the potential for pain relief from sympathetic nerve block usually indicates an early trial of this approach.

Complex regional pain syndrome can occur in the medically ill (87), and when it is suspected, sympathetic nerve block is usually considered. Some patients are too ill to undergo this procedure and many receive no benefit (complex regional pain syndrome without sympathetically maintained pain). For these patients, drug therapy becomes the usual mainstay approach. Those who do not respond adequately to an opioid may be offered any of the drugs used for neuropathic pain, as described. Additionally, some drugs have been used specifically for this diagnosis (88). There is some evidence from controlled trials that calcitonin-salmon, corticosteroids, and bisphosphonates may be effective (88,89). Other drugs are tried based on anecdotal observations. Trials of sympatholytic drugs, including peripheral a-antagonists (e.g., phenoxy-benzamine hydrochloride and prazocin hydrochloride), central a-agonists (e.g., clonidine hydrochloride), and B-antagonists (e.g., propranolol hydrochloride) may be considered for patients who cannot undergo neural blockade. Other patients may be offered trials of a calcium channel blocker (e.g., nifedipine) again based on anecdotal observations.

Adjuvant Analgesics for Bone Pain

Malignant bone pain may respond adequately to therapy with an opioid, or an opioid in combination with an NSAID or a corticosteroid. Radiation therapy is usually considered when bone pain is focal and responds poorly to opioid therapy, or is associated with impending pathological fracture. Multifocal bone pain that responds poorly to an opioid trial may benefit from treatment with an adjuvant analgesic. These drugs include bisphosphonate compounds, calcitoninsalmon, gallium nitrate, and

bone-seeking radionuclides.

There have been no comparative trials of these adjuvant analgesics for bone pain. Based on the abundance of supporting evidence, the benefit to nonpainful skeletal comorbidities (e.g., fracture rate), and convenience, the bisphosphonates are generally preferred as the first-line approach. There is strong evidence that certain bisphosphonates, including pamidronate disodium and clodronate, can be analgesic, reduce fracture rate, and improve quality of life (90,91,92 and 93). Pamidronate is available in the United States and usually is administered via brief infusion at a biweekly dose of 60 mg or a monthly dose of 90 mg. Side effects are usually mild and consist of flu-like symptoms and injection site reactions (94); the oral drugs are associated with esophagitis, which can be treatment limiting. Newer bisphosphonates are in development and will further increase the convenience and safety of this approach. The cost of these drugs is relatively high, and although the cost benefit may be favorable given their effectiveness in reducing skeletal comorbidities, further studies of the pharmacoeconomic aspects of bisphosphonate therapy is warranted (95).

The data supporting the use of calcitonin-salmon (96,97 and 98) and gallium nitrate (99) are very limited. Experience with calcitonin-salmon may warrant a trial in patients with refractory multifocal bone pain. Evidence is much better for the bone-seeking radiopharmaceuticals, strontium-89 and samarium-153 (100,101). These drugs should be considered for patients with refractory multifocal pain caused by osteoblastic lesions or lesions with an osteoblastic component. Samarium-153 allows imaging with bone scintigraphy during treatment for bone pain. Patients who receive these drugs should have life expectancies greater than 3 months, adequate bone marrow reserve, and no further planned therapy with myelosuppressive chemotherapy. Patients with a platelet count below 60,000 or a white blood cell count below 2400 generally should not be treated. The onset of effect is often slow (2 weeks or longer), and peak effects may not be attained for more than 1 month. Some patients experience a flare of pain before analgesic effects occur. The chief adverse effect is bone marrow suppression, with thrombocytopenia that may be irreversible. Patients who tolerate the therapy but experience a return of pain can undergo repeated administration.

Adjuvant Analgesics for Bowel Obstruction

Patients with malignant bowel obstruction who are not candidates for surgical decompression require intensive palliative interventions to reduce pain and other obstructive symptoms, including distention, nausea, and vomiting. Evidence-based guidelines have begun to clarify the role of nasogastric suctioning, venting gastrostomy, and pharmacotherapy for symptoms in populations with advanced cancer (102).

Although controlled trials with symptom end points are very limited, there is wide acceptance of a role for cortico-steroids, anticholinergic drugs, and somatostatin analog (e.g., octreotide acetate) in the treatment of bowel obstruction (102,103,104,105 and 106). The optimal use of these drugs may minimize the number of patients who must be considered for chronic drainage using nasogastric or percutaneous catheters.

Corticosteroid therapy may relieve obstruction in some cases, or merely reduce symptoms (107,108). The specifics of the treatment, including the drug and the dosing regimen, are currently empiric. Dexamethasone is commonly used and treatment typically involves a low-dose regimen, or a modest loading dose followed by a low-dose regimen. One case series, for example, described the use of dexamethasone in a dose range of 8–60 mg/d (106).

Anticholinergic drugs presumably relieve the symptoms of bowel obstruction by reducing motility and intraluminal secretions (109,110). Scopolamine hydrochloride or scopolamine butylbromide, hyoscyamine, and glycopyrrolate have all been used in practice. The use of a quarternary compound, such as scopolamine butylbromide or glycopyrrolate, is likely to reduce the potential for centrally mediated side effects from this approach. Dosing with each of these drugs is empirical. Low initial doses are usually titrated cautiously until benefit occurs or patients begin to report uncomfortable side effects.

Patients with refractory pain from bowel obstruction may also be considered for a trial of the somatostatin analog octreotide acetate. This drug inhibits the secretion of gastric, pancreatic, and intestinal secretions, and reduces gastrointestinal motility. Like the anticholinergic drugs, the use of this compound in the symptomatic treatment of bowel obstruction is now supported by case series and small, randomized trials (102,109,110). In practice, treatment has been implemented by repetitive subcutaneous dosing or by continuous subcutaneous infusion. Doses must be titrated to effect and typically begin at approximately 0.3 mg/d.

CONCLUSION

Translational research has yielded numerous advances in the pharmacotherapy of pain during the past three decades. Although opioid therapy continues to be the mainstay approach for the management of moderate or severe pain in patients with serious illness, the outcome of opioid therapy is not uniformly favorable and clinicians must understand a range of alternative analgesic strategies. The appropriate use of nonopioid and adjuvant analgesics represents one such strategy, which may have particular benefit in those populations with neuropathic pain, bone pain, or pain associated with bowel obstruction. Clinical research is needed to further establish the analgesic effects of the many new drugs that are now being used empirically. Comparative trials are needed to provide guidance on the selection of specific therapies in future.

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5

NONPHARMACOLOGIC MANAGEMENT OF PAIN

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Progress has been made in the pharmacological treatment of cancer pain in the past decade. Yet many cancer patients continue to receive inadequate pain care, despite increased awareness of the public, extensive physician and nurse training, guidelines, regulations, and increased use of opioids by oncologists (1,2,3,4,5 and 6). Even carefully implemented clinical trials or specialist consultations indicate that pharmacological or invasive treatments do not eliminate all cancer-related pain, but rather make it manageable for most patients (4,7). Other explanations for less than complete pain relief include entirely nonmedical reasons: reluctance of patients to take prescribed medications because of fears of side effects or addiction, reluctance of patients to discuss their pain, inadequate assessment, inadequate knowledge of patients about what is appropriate to discuss and treat, myths that disrupt communication between patients and health care providers, and real-world limitations such as cost or accessibility of medications (8,9 and 10).

As the vast majority of patients are treated in ambulatory clinics, their adherence to treatment cannot be assumed. They leave appointments to return home and treat themselves, or not. Because patient factors can entirely undo an optimal treatment plan and some pain usually remains unrelieved even with the best treatment, knowledge of nonpharmacologic approaches is required not only for specialists, but for all clinicians who treat patients with cancer pain.

Although pain experts recognize that barriers to management of pain exist and that nonpharmacologic methods can be as effective as more invasive treatments in some circumstances, there is little to guide the clinician in how to practically integrate these methods into the day-to-day demands of a busy medical practice. The basic question becomes not *should* we use nonpharmacologic techniques, but rather *how* can we use them to our patients' best advantage within the realistic parameters of today's health care.

In this chapter, we review nonpharmacologic methods all clinicians need to integrate into their practice of cancer pain management. We focus particularly on simple, yet effective, communication and education methods that can be used in any medical practice by any professional treating a cancer patient with pain. We then add brief information on physical methods of pain relief and more specialized cognitive-behavioral approaches used by psychologists and other behavioral medicine specialists. Additional information on assessment, rehabilitation, physical, music and art therapy, and complementary and alternative treatments can be found in Chapter 1,Chapter 2,Chapter 4, Chapter 70, Chapter 72 and Chapter 73.

BACKGROUND

As everyone working in oncology recognizes, cancer patients have all types of pain, from brief but repeated procedures, to time-limited surgical-, chemotherapy-, or irradiation-induced pains, and for many patients the addition of progressively worsening disease-related pain. Within this diversity, it is not surprising that different strategies are needed for different types and durations of pain. Moreover, patients who experience different pains, usually accompanied by other symptoms, can be expected to have thoughts, feelings, and behavioral reactions to both experienced sensations and the anticipation of further discomforts. Although standard pharmacological approaches primarily treat the existing sensory component of pain, nonpharmacologic approaches can treat all the dimensions of pain including sensory, cognitive, affective, and functional. In this context these strategies also offer patients a method for taking more control of their experience and for moderating fearful anticipation of treatments or increased pain that can in turn escalate their pain experience (11,12).

Nonpharmacologic approaches rarely replace pharmacological or invasive treatments; rather they are an essential component of any adequate treatment. Nonpharmacologic strategies become tools to assist the clinician in addressing stumbling blocks that impede care, or these methods can provide options for improved patient comfort with no side effects.

One caveat to selecting nonpharmacologic treatments is that they generally require patients to be active participants in their care. Most methods are based on verbal communications that require patients to have some motivation, to sustain attention, and to provide some feedback. All non-pharmacologic methods work best when they are used early in treatment as a part of a comprehensive treatment plan, not after everything else has failed and patients are worn out and distracted by severe pain. When employed early in care, nonpharmacologic approaches can optimize the effectiveness of all other medical treatments.

These strategies are intended for use with any patient who is experiencing discomfort. Because we know that psychological factors are influential, but not causal in the maintenance of cancer pain symptoms (11,13), we know that most patients can benefit from these strategies, not only those patients in psychological distress or those who have psychiatric diagnoses (14,15). Of course, those patients who are in continuous, severe, disease-related pain need aggressive medical treatment before use of nonpharmacologic methods (5). Similarly, patients with delirium or severe psychiatric disruption in their functioning will need additional care beyond the methods discussed here.

ADHERENCE TO MEDICAL TREATMENT

Lack of adherence to treatment is recognized as threatening the health and even survival of patients, and analgesics are included as an area of major concern for unsafe treatment (16,17). From 1983 to 1993 all-cause outpatient deaths from medication errors increased more than 800% while the number of outpatient medical visits increased 75% (16). In spite of the attention recently to medical errors, adherence to cancer pain treatment by well-intentioned patients and physicians is an under-recognized problem. Although cancer patient adherence may be nearly complete with chemotherapy, pain treatment is rarely so well defined. Most patients are given relatively loose parameters for medications, leaving them free to adjust dosing as needed. Patients act on their own beliefs or their families' beliefs; they adjust doses, skip doses, and simply stop taking a medication because they do not like a side effect. Increasingly patients do not even fill prescriptions because costs are not covered by insurance. Physicians usually do not hear about this unless they specifically ask about cost coverage or actual medication behaviors of patients. Conversely patients may take too much medication simply because they do not remember to stop one drug when another is started. We commonly see patients on multiple nonsteroidal antiinflammatory drugs or opioids, without a clear idea of what the medications are for. Adherence data indicate that about 40% of cancer patients do not take their pain medications as prescribed (18). The same data indicate that adherence is a significant factor in level of pain; better adherence improves pain relief.

Although extensive discussion has taken place regarding the need for increased training of physicians, nurses and pharmacists, far less effort has been directed toward under-standing patient and family training needs. The literature on adherence makes it clear just how difficult this area is to assess, much less to intervene. When patients' beliefs do not fit what we tell them to do, they often will not argue or even ask questions, but will nod their heads and then proceed to act on their beliefs or concerns (18,19).

When asked why they do not ask more questions, patients say, “I don't really know what to ask,” or “There are so many possible questions that I don't know where to start or which ones are important.” Furthermore, as with all of us, when we think we know an answer, we don't ask the question. Along the lines of the classic “We don't

know what we don't know," patients have said: "I know they save morphine until you're dying," or "I know morphine is addicting." The physician will never hear a question from these patients who think they already know. Unless clinicians ask directly, they will not know that these thoughts are on a patient's mind, but the patient will do whatever he or she can not to take morphine.

The past decade of research has clearly established the importance of beliefs in influencing pain treatment behavior, the difficulty patients have in knowing what to ask their physicians or nurses, and the strong resistance patients have to taking more pills, especially pills that cause side effects. These factors have led us to conclude that we, as clinicians, must take more initiative in raising those concerns that we know are important in determining patient outcomes.

COMMUNICATION INTERVENTIONS FOR ALL CLINICIANS

Communication is the most basic intervention used in patient care. At a time when illness-related concerns become the focus of patient and family thinking, communications with the medical staff are given enormous significance. Words and behaviors are repeated, over-interpreted, and scrutinized for underlying messages. Families use medical team words as a primary source to define their unspoken and spoken rules, beliefs, and behaviors (20). Research has demonstrated that effective communication between physician and patient can lead to improved health outcomes (21). Nurses and physicians routinely convey information, they listen, they reassure patients and family members, and they actively educate patients about both the pain and potential treatments. Each of these interactions can enhance patients' beliefs in their ability to cope with the symptoms they have, can foster adherence to the medical plan, or conversely, can escalate patient fear or helplessness, often without signaling the medical team that this is happening.

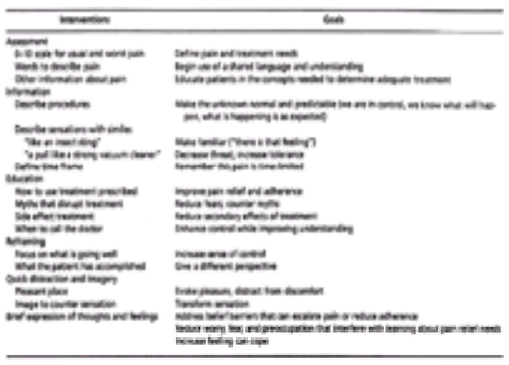
Patients turn the words of the medical team into internal "cognitions" or thoughts which either increase fear or provide reassurance when they have pain or other unfamiliar experiences. When medical team members are aware of the types of communication they are providing, they can positively influence these cognitions. When they remain unaware of the importance of their words, an opportunity can be lost or a valuable tool can be unintentionally misused. One of the contributions clinicians can make to the long-term mental health of patients and their families is to model, by example, the acceptability of talking about and planning for pain management, disease progression, and death.

Standard Practice Tools

In order to provide comprehensive pain management, the following communication tools should be understood by all clinicians:

- Assessment of pain and concurrent symptoms
- Provision of information
- Interactive methods of education
- Reframing within standard care
- Quick distraction and imagery for unpredictable or procedure pain
- Brief expression of thoughts and feelings

Table 5-1 lists examples and intentions of these methods. All clinicians can use these in everyday practice. Their use may take a few extra minutes at first, but will save extensive time and distress required by patients who misunderstand, resist necessary care, or require more time and more visits from symptoms that are uncontrolled. Used with awareness, these strategies can be strikingly effective in making care easier while helping patients manage their pain.



Interventions	Goals
Assessment	
0–10 scale for usual and worst pain	Define pain and treatment needs
Words to describe pain	Begin use of a shared language and understanding
Other information about pain	Educate patients in the concepts needed to determine adequate treatment
Information	
Describe procedures	Make the unknown normal and predictable (we are in control, we know what will happen, what is happening is as expected)
Describe sensations with similes	
"like an insect sting"	Make familiar ("there is that feeling")
"a pull like a strong vacuum cleaner"	Decrease threat, increase tolerance
Define time frame	Remember this pain is time-limited
Education	
How to use treatment prescribed	Improve pain relief and adherence
Myths that disrupt treatment	Reduce fears, counter myths
Side effect treatment	Reduce secondary effects of treatment
When to call the doctor	Enhance control while improving understanding
Reframing	
Focus on what is going well	Increase sense of control
What the patient has accomplished	Give a different perspective
Quick distraction and imagery	
Pleasant place	Evoke pleasure, distract from discomfort
Image to counter sensation	Transform sensation
Brief expression of thoughts and feelings	Address belief barriers that can escalate pain or reduce adherence Reduce worry, fear, and preoccupation that interfere with learning about pain relief needs Increase feeling can cope

TABLE 5-1. COMMUNICATION INTERVENTIONS USED BY ALL CLINICIANS

Assessment Provides a Shared Language for Patients and Clinicians

Pain assessment is the cornerstone of both pharmacological and nonpharmacologic intervention. Inadequate assessment is the first step toward inadequate treatment (9,22). Adequate assessment is an essential step to effective treatment and to facilitating patient adherence. Proper pain assessment begins the process of communication that determines medical treatment, and also begins to teach patients how to think about and report their pain. By asking the same questions at each assessment and giving the patient some options for answers, the physician and patient begin to develop a common language for communication, e.g., "Does your pain feel like burning, shooting, or pins and needles, or is it an aching, sharp, or throbbing kind of pain?" Patients begin to recognize different qualities in their pain. Physicians begin to determine whether intervention should be oriented to neuropathic and/or nociceptive treatments. In our recent study of an educational intervention for cancer-related pain (23), a patient called to thank us profusely for "teaching me so much about pain—it changed my life and gave me a mission for the time I have left." We of course thanked her for letting us know. We then became puzzled when we realized that she was in the control group that did not receive pain education. When we called her and asked what had been so helpful, she told us how she learned so much from assessment of her pain in the study, that it changed the information she gave her doctor and this changed her treatment, bringing her far more pain relief.

Information Provides Familiarity and Predictability

Whenever possible, it always helps to make the unfamiliar more predictable by informing patients of what is going to happen. This can be very reassuring for patients because uncertainty is known to increase distress and threaten perceptions of ability to cope (24). Yet, the informed consent process used in many clinics emphasizes provision of medical information that patients often do not fully comprehend (25). The legally required process of reviewing risks forces patients to recognize the limits of their own, and the medical staff's, control over the outcome of treatment. Although this process is necessary and valuable to patients, the emphasis on uncertainty can increase patient and family distress related to what is unknown and unfamiliar. This can decrease self-efficacy, the belief that one has the ability to manage the difficulties one faces. Of all psychological concepts related to pain, none are as consistently and significantly shown to influence pain level and treatment outcome as elevated distress and lowered self-efficacy (11).

Some of the effects of this informed consent process and the overall uncertainty about what will happen can be countered by providing specific information about what is known. Information can help patients to "label" their sensations with familiar, less frightening terms. Information also gives patients a way of "reframing," thinking about their situation from a less threatening or more incontrol perspective.

Three kinds of information are helpful to patients:

1. Describing procedures, risks, and benefits (informed consent)
2. Describing predictable sensations
3. Defining the duration of each predictable sensation

Describing procedures provides patients with specific information about what will happen. By giving patients a concrete description of the steps that will occur, patients can later remind themselves that what is happening is expected. In describing what will happen it is essential to include the benign steps in this description, ("You'll sit on the bed and bend your back. We'll clean your lower back with antiseptic.") not only the invasive steps ("We'll stick a needle into your pelvic bone.") This helps patients mentally balance the event in a way that reminds them that most of what is happening is unthreatening. When patients know what to expect, the amount of uncertainty is reduced, which in turn increases confidence that the situation is under control.

Describing sensations helps patients because it tells them exactly how they will feel. By using specific descriptions, patients are able to label what they feel with familiar sensations. Vague terms, such as *pain* or *hurt*, leave patients worrying about how much pain and whether they will be able to tolerate it. Even something unpleasant can be made less threatening by associating it with something familiar. Describing a sensation as “like a bee sting” or “a heavy pressure” does not deny discomfort; rather it allows patients to prepare themselves. When these sensations occur, patients are able to reassure themselves that these are expected and familiar. Use of a simile can be particularly helpful when describing a sensation and reminding the patient that the experience is tolerable. For example, “When I pull the marrow out you may feel a sharp pull all the way down your legs as if a strong vacuum cleaner is tugging from your back down your legs.” Although the feelings are not pleasant, the experience of them—if predicted—can be reassuring.

Defining time frame may be the most useful type of information clinicians can provide, particularly with pain resulting from procedures or treatment (26). For most people, knowing there will be an end makes an unpleasant event much more tolerable than thinking it might last forever. It is particularly helpful to break the events into the smallest time frames possible. So, for instance, we do not talk about a bone marrow aspiration as taking “only 20 minutes.” We break the aspiration down into sections. The local anesthetic might take 30 seconds; the pressure of the needle going into the bone marrow might take 5 seconds; feeling of the pull might take another 10 seconds. Although the overall procedure might take 20 minutes including preparation, we help patients to recognize that the painful section lasts less than 2 minutes, and that most of the procedure is not painful at all. For any of us, our belief in our ability to tolerate 2 minutes of pain is much greater than our belief that we can withstand 20 minutes of intense pain.

In general, procedural information is the most frequently provided, however, it is typically less useful in reducing worry and discomfort than temporal or sensory information (27,12). Sensation and procedure information provided in combination have been shown to be superior to sensory information alone in the reduction of pain and distress (28).

Ideally, patients receive all three types of information for the greatest effect on pain and distress. To familiarize and normalize the experience all information must be provided before beginning a new process. During a treatment or procedure, the focus should usually shift to active distraction, imagery, or storytelling so thoughts are focused away from discomforts that cannot be alleviated. Although it is tempting to ask patients if they are hurting, this refocuses attention on pain and can entirely undo the benefits of distraction strategies. It is ideal to make a plan before starting for how the patient will let a clinician know if pain is too intense by lifting a hand or another signal. This allows both the patient and whoever is assisting in distraction to continue with imagery or storytelling while letting clinicians know that pain has increased and may require additional analgesic.

For the small number of patients who are phobic of a procedure or who need to remain vigilant, systematic desensitization can be done with very short-term treatment and is effective if sedation is not appropriate. These patients need to receive constant feedback from the clinician doing the procedure about what is happening and what they can expect of sensations and time frame. Additionally, these patients need to control the timing of the procedure whenever possible. With highly anxious and control-oriented patients, there is a tendency for physicians and nurses to want to get the procedure over with as quickly as possible to reduce the patient's distress. They sometimes push ahead as fast as possible while the patient fights all the way. It does initially take longer to slow down and give patients time to maintain their control, and to let them set the pace. However, if this extra time is taken with these infrequent patients, the long-term trauma and the resistance to further treatment will be far less.

Education

Although information provides facts, education requires an interactive process in which patients learn and then use their new knowledge to direct their own behavior. Education does more than label an experience, it allows patients to take the information presented to them, adapt it to their changing situations, and then adjust their thoughts and behaviors accordingly. Education involves both the telling of facts, training of how to accomplish a goal, and brief addressing of patient questions, concerns, and problem-solving potential obstacles. For reluctant patients or those with strong beliefs, adherence can be greatly aided by asking patients what they will do when they have pain and then problem-solving any remaining barriers. This rehearsal can facilitate patient adherence to treatment and can point out to the clinician where the patient may have difficulty implementing the plan.

Clinicians are often frustrated by patients who are given information, but seem not to hear it. Anxiety, unfamiliarity, and the numerous amnestic medications used in cancer treatment may impact patient ability to retain seemingly learned material. Research indicates that opioids, although they have minimal effects on most areas of function, do affect long-term retention of new information (29,30). Although patients may appear to comprehend information during their office visit, they may not be able to recall the information later at home. In addition to these physiologic aspects of learning interference, the distress and helplessness brought about by a cancer diagnosis, compounded by the experience of pain, can disrupt long-term retention. Recognizing these limitations, it seems an obvious solution to write down important instructions or details so they can be recalled later. It helps to have standard practice prescribing sheets and pain report forms so this information does not have to be written anew each time. Some examples of standard written tools that can be adapted to individual clinical settings are in Appendix 5-1. Diaries can also be used to track pain level and medication use.

Education has conclusively demonstrated improvement in many medical outcomes, including pain, in many types of patients. Recently, clinical trials have demonstrated the effectiveness of education as a tool for cancer patients with progressive, disease-related pain (23,31,32 and 33). In a randomized controlled trial we conducted with adult cancer patients, all participants watched a videotape, reviewed a printed handbook, and received brief nursing training tailored to their needs, which lasted about 15 minutes (23). Patients were randomized to either a pain or a nutrition active control group. Patients who received the pain training demonstrated significant increases in their knowledge about cancer pain barriers and, more important, they reported 25% declines in pain report when compared to the nutrition group 1 month later. These improvements remained in 3-month follow-up, although no intervention was provided differentially to physicians and nurses of these patients. The improvements occurred despite the fact that research nurses were not available to apply the patients' training in future appointments. It seems likely that the results of the education and patient training could only be strengthened if implemented by clinic nurses and physicians who will be at the patients' next appointments to reinforce the training. Oliver and colleagues (32) similarly found pain intensity improvement with brief individualized patient training, and DeWit et al. (31) reported decreased pain with a multi-method, pain education program. Further demonstrating that education methods are effective across sites and populations, in a study targeted to elderly patients with cancer and their family caregivers, Ferrell et al. (33) evaluated a structured pain education program during home care visits with elderly patients and found improvement in knowledge, attitudes, and compliance.

With time demands on practice, it is important to note that written materials and videos are effective strategies for reducing the face-to-face interaction time with nurses or physicians. Numerous booklets, books, and videotapes are available to use as educational tools with patients, and data consistently indicate that patient training should be incorporated into routine oncology practice (1,33,34,35,36 and 37). Written materials are useful because they reduce the burden of having to retain information solely in memory. However, we are aware of no data to indicate that print material or videotape alone is effective in improving pain outcomes, without some review and tailoring to the patient's needs. Specific education needs of patients and their family members are listed in Table 5-2. These targets for education should be addressed when disease-related pain is mild and when opioids are first needed. At that time patients are interested, motivated to take charge of their care, and usually have the energy to focus and learn new information and strategies. If patients are in severe pain or have other major symptoms, training will be more effective if held until symptoms are better controlled (5).

TABLE 5-2. EDUCATION NEEDS OF PATIENTS AND FAMILY MEMBERS

Reframing

Reframing offers a fresh, more capable, and less catastrophic look at a difficult situation. When cancer patients experience numerous bad things, and then have

recurring or persistent pain, it is not surprising if they begin to feel that nothing they do makes a difference, that their efforts are useless, and that the pain—along with everything else—will keep getting worse. Reframing means, quite simply, changing the perspective one has on this situation, thus shifting the way one thinks and feels. This shift in perspective reduces the threat without denying realities. Reframing generally implies changing a fearful thought to a neutral or positive thought.

However, reframing may not be needed if the original framework is adaptive. If clinicians remember that their words will be retained and repeated over and over by patients and families, and if they use this fact to actively select communications to facilitate capable, self-efficacious patient and family perceptions, this will be one of the simplest and most helpful strategies for managing the distress and fear related to cancer and pain. Although most patients and families look for statements that offer hope, they also hang on to negative information. It can be extremely valuable, when providing feedback about the patient's condition, to include statements about what is going well medically, without being misleading, and to recognize some action of the patient that warrants praise. Specific positive accomplishments are always possible to find.

The process of framing or reframing does not change most of what clinicians do in communication with patients. When entering a patient's room, symptoms, problems, and patient concerns can be addressed first. This allows patients to express concerns and helps validate their experiences. Next, patients can be asked about symptoms the clinician believes they do *not* have and then about what they have been doing in activities. Finally, to reinforce what has just occurred, the clinician can comment on the many accomplishments of the patient and family and on those areas of functioning that are not problems. For example: “You've been able to walk a little bit each day, that's wonderful, that's the best thing you can do to keep your strength.” For a very ill patient for whom getting out of bed is a huge effort, the acknowledgment may be quite different: “You've been able to get a bath today, that's great; I know that must have taken a lot of energy and effort.” Although the accomplishment may seem quite small, the patient knows how much energy the activity took and will appreciate having this recognized.

With this strategy the clinician can acknowledge the problems that are of concern to patients and their families, while also honestly helping them to recognize that, no matter how difficult the situation, there are things that are not problems, and they are doing a good job of managing a very challenging situation. This simple, positive perspective can do much to contribute to feelings of control, self-efficacy, and reduction of fear for patients and their families.

One key to remember in giving people bad news is that nearly all people can deal with anything, even death and pain, if they feel capable and like they are doing a good job in managing a situation anyone would find difficult. Reminding others or even ourselves that we still have control in some area and are doing well at controlling what we can helps virtually all of us to feel that we can manage our problems.

In summary, the process of reframing is to

1. Acknowledge, validate, and respond to the problems.
2. Widen the perspective to include medical areas that are not problems and to include specific accomplishments of the patient.
3. Give the patient credit for an accomplishment so that the patient feels recognized and proud of what he or she is doing.
4. Whenever possible remind the patient that the situation today is not forever and define the time frame if it is known or can be estimated.

Reframing as a strategy has not been tested on its own in clinical trials. Still it is the foundation of cognitive-behavioral training in coping with anything mentally or physically painful. In this training, the model is to learn to observe thoughts and feelings that make a person feel worse and shift these thoughts to more adaptive, less out of control thoughts that assist anyone to feel better and adapt more effectively to problems. With the reframing described in this section, clinicians offer patients the results that contribute to this effective thinking without taking time beyond that required for adequate care.

Quick Distraction and Imagery

Distraction can take many forms when dealing with pain. Many types of distraction have been used effectively, such as focusing on breathing or relaxing, doing math, counting ceiling tiles, saying a poem, meditating over a calming phrase, doing massage, and listening to music.

Clinical trial data clearly demonstrate that imagery/hypnosis is the most effective of cognitive strategies, with little data to clearly distinguish the efficacy of imagery versus hypnosis (15,38,39). With intense pain that is not driven by tension, active imagery is most effective when it engages as many sites and senses in the brain as possible in processing information.

When pain is of brief duration and/or medical treatment can not reduce discomforts, most patients can be assisted in placing their attention elsewhere by using imagination. This can be accomplished easily through using simple strategies such as talking with patients about a pleasant experience they have had. Having patients tell you stories about an experience helps to engage patients away from their discomfort. Talking requires more focus and more brain occupation than just listening. When using this strategy, it is important to elicit a memory of a place where patients have felt particularly at ease and happy but also active. For example, you can ask patients to tell you about a favorite vacation, or another favorite place they most enjoy being. Rather than lying on a beach and relaxing with their imagery, encourage them to share as much detail as possible: what it looks like, the sounds, the feelings, the temperature, and especially the activities they do there. Memories of physical activity can help to block pain processing similar to actual activity if the bodily sensations of that activity are evoked. Patients can become so engrossed in the reliving of that experience that they become unaware of their pain in the present moment. Recounting these positive events reintroduces feelings of pleasure as well as providing distraction. These in turn counter perception of pain.

Brief imagery also can be used to counteract the sensory qualities of intense but brief unpredictable pain. To change the pain itself, we take the patient's description of sensation and create an image to counter this sensory quality. For burning, stabbing pain we might have the patient focus on deep breaths while imagining blowing freezing arctic air through the sensation. With extreme pressure pain, we might use an image of a heavy load of bricks lifting off the painful area, lifting higher and feeling lighter with each exhale, until the patient can float away from that pressing, heavy feeling. At the most intense time during procedures, we insert into any distraction the image of blowing up a balloon, blowing hard with the patient, mentioning the pressure in the cheeks, and asking what kind of balloon, what color, what shape. At these points, it is also helpful to raise one's voice and speak more rapidly, along with increased pressure on a shoulder if appropriate, and any other shift that pulls attention to the images and voice of the clinician.

Control of breathing is a natural part of most imagery and is usually the first step toward reducing the tension associated with pain. Focus on breathing also begins the process of focusing away from the pain perceptions.

For quick and easy imagery or distraction, the following components are helpful to keep in mind. Have the patient choose an image or participate in the selection so that it is relevant. For intense pain, an image that includes physical action by the patient will be more engaging of attention than a passive, purely relaxing image. Having the patient talk, rather than just listen to you, maintains the patient's focus far more effectively. Sound made by the patient, whether talking, breathing out through the mouth with a “whooshing” sound, or any other sound, counters acute pain better than silent imagination. Adding a physical stimulus will help counter the pain stimulus. This can be squeezing the shoulder, having the patient squeeze your hand, having a family member massage feet or hands, or including physical stimulus within the imagery. It is optimal to provide pressure at a location between the pain and the spinal cord. The goal is to create as much input into the brain as possible, to flood the brain with nonpain messages and thus prevent the pain message from being processed.

Brief Expression of Thoughts and Feelings

Presence of distress, especially distress specific to the pain or cancer situation, will contribute to a patient's perception of pain (11). For patients who are acutely anxious about a procedure, or who are generally anxious about their pain or cancer, a chance to express their thoughts, concerns, and feelings is essential before continuing with any of the nonpharmacologic methods described above, and for maximal efficacy of pharmacological methods. The fact is that patients who are preoccupied will not hear information, will not learn what they need to about their treatment, will not hear reframes, and will not benefit from the distractions of imagery or massage. As a consequence they will have more difficulty following prescribed medical treatment. These will be the patients who require more effort and time at each visit and will have poorer pain relief. Ten minutes of expressing feelings and addressing of concerns can save numerous future appointments and can contribute significantly to improved outcomes (13,40). As we discuss below in the section Structured Support and Psychological or Psychiatric Referral, talking and expressing concerns in a supportive setting has been nearly as effective as more advanced techniques in relieving cancer pain (14,15).

Sometimes people just need to know that they have been listened to and understood. Cancer patients who are fearful for their life or future sometimes just need to have a chance to have those fears and concerns acknowledged. Angry, upset patients and family members can be difficult to deal with, especially if they are coping with their fears by accusing health care providers of not being helpful. One of the best ways to diffuse an angry or potentially explosive situation is to allow this expression of upset, followed by an acknowledgment that you have heard them, will do what is possible, and will be available to discuss further, if needed. An expression of empathy, “Tell me about what happened … I can see that this has been difficult and upsetting for you. Let's see if we can do something that will make things better. Do you have ideas about what we might do?” This is not the same as colluding with the patients' anger; rather it facilitates communication, by assuring patients that their experiences and thoughts have been heard. By this expression, it allows you and the patient or family to move past the hurt feelings. For very demanding and difficult-to-control families, a regularly scheduled meeting to go over care and concerns can save more time than recurrent unpredictable demands that result in a need to meet more often or at times that are ineffective in addressing the overall care of a patient. Treating a patient's pain and suffering must include

addressing suffering on multiple levels, including that patient's fears and anger (41).

PHYSICAL AND COMPLEMENTARY METHODS

Thus far, we have focused largely on verbal methods of relieving pain. Physical methods, such as massage, ice and heat, as well as music therapy, are also nonpharmacologic techniques that allow patients and family members to participate in providing pain relief, thereby increasing their sense of control. Although few randomized controlled clinical trials exist to establish the efficacy of these methods (1,42,43), a nascent literature and clinical reports indicate that these techniques are received well by patients and are reported to provide some relief (33,42,44,45). Despite the dearth of experimental evidence for many of these strategies, patients are often receptive to these methods. It is use-ful for clinicians to have some knowledge of the pros and cons of using these approaches. Advantages of these methods are that they provide physical contact for patients, they have few (but can have some) side effects, and they give family members an opportunity to be involved, while at the same time they may directly reduce pain.

Massage may be most easily accepted by patients, requires minimal preparation, and can be easily implemented. It generally requires another person willing to assist, although mechanical massagers can be used. It is noninvasive and can be performed by health care professionals or family members. Professionals trained in therapeutic massage may achieve greater efficacy beyond relaxation and distraction. In a randomized controlled trial examining the impact of massage therapy during high-dose treatment, patients who received 20-minute sessions of shoulder, neck, head, and facial massage had lower levels of cancer-related symptomatology, but not lower pain, than those who did not receive massage (42). Foot massage or reflexology has also been the subject of study and has been shown to reduce cancer pain, nausea, and anxiety (43,45). Use of a lotion, massage oil, or powder helps reduce friction on the skin. Movements should almost always be continuous, even, and rhythmic (52). If provided by family, instruction should include the importance of feedback from the patient and making sure that massage is not painful. Generally, massage should not occur directly over a tumor location or directly over a pain area, but rather proximal to the pain or tumor or in another area of the body altogether. Health care providers using massage for pain treatment should have appropriate training and licensing for both efficacy and legal reasons.

Choice of heat or cold and of the method used depends largely on trial and error. As a rule, patients are more easily convinced to use heat than cold, but cold can be as effective, or more effective, and relief may last longer (33,47,48). Alternating between heat and cold can also be an effective option. Applying heat can be done with hot water bottles, electric heating pads, hot moist compresses, bath, or whirlpool/hot tub. Applying cold can be done with ice and water combined in a waterproof bag, terry cloth filled with ice and wrung out, frozen gel packs, or bags of frozen corn hit to gently loosen contents. All options should be sealed to prevent dripping, wrapped as needed to prevent skin irritation or burning, and should be flexible to conform to body contours. Location directly on the pain, proximal, distal, or contralateral to the pain is a question of trial and error and patient tolerance (46). Patients should be instructed to stop when the area becomes numb, excessively red, blisters, or when they want to. Time of use to be effective ranges from 5 to 30 minutes. Patients should not sit or lie on the heat or cold packs. Heat should not be used directly over tumor sites (1). Other contraindications include use over a recent radiation therapy site where skin may be more sensitive, if bleeding is occurring, if patients have impaired sensation, or if skin blanches and turns red after the application of cold.

Music Therapy

Use of music to relieve suffering and pain has grown in popularity over the past few years. A few randomized or other experimental trials indicate some success in relieving pain. Certainly no harmful effects have been indicated (49). However, most of the literature remains anecdotal (50,51). The most careful research indicates that music therapy is about equivalent to relaxation training in efficacy for pain treatment (44,49). Numerous different styles of music therapy have been used, and success may vary depending on what method is used. However, to our knowledge these distinctions have not been tested. Music can be played for patients, patients may select their own music then change music depending on preference, and, alternatively, patients can make their own music using simple instruments. Two suggestions are most clear in methods for music therapy as a pain and suffering treatment. One is to have patients select their own music rather than having it given to them or to all patients at once in a particular setting. Another is that for effective use, a clinician should at minimum read about how to use this method and preferably should receive training in using music therapy. For more on music and art therapy, see Chapter 72.

Specialized Cognitive-Behavioral Interventions

There are times when medications and brief strategies are not adequate to manage a chronic or recurring pain, and invasive strategies are inappropriate. These circumstances include those in which distress or depression are substantially elevated, in which a history or active substance abuse complicates treatment, when panic or phobia contribute to procedure discomfort, or when a situation requires expertise in imagery or hypnosis. At such times, it is appropriate to consult with a psychologist or other behavioral medicine specialist who can provide more specialized cognitive-behavioral pain management techniques. Table 5-3 lists strategies used most often by psychologists, social workers, nurses, or psychiatrists after specialized training in these skills for pain treatment. Because most of these are methods that can be taught to the patient for use when a therapist is not present, they can be excellent methods for increasing coping options, self-efficacy, and self-control of pain. Most practitioners combine the techniques described in the following sections into a package of coping skills integrated with medical treatment, not as alternatives to medical treatment (14,15,52).

Intervention	Assists with
Relaxation/imagery/hypnosis	Possible neuroendocrine changes
Relaxation	Reduction of autonomic arousal and tension
Progressive muscle relaxation	Learn to identify and change tension
Deep breathing	Learn control over somatic states
Imagery/hypnosis	Mental activity competes with pain
Pleasant places	Introduces feelings incompatible with pain
Analgesic images	Blocks pain sensations
Reframing and cognitive-behavioral training	Reminds patient that situation is manageable
	Balances positives with negatives
	Reminds patients of their competence when learning to do for themselves
Distraction	Stimulation competes with pain sensations
Focus on mental activity	Blocks attention to pain
Focus on physical activity	Addition of pleasure to daily experience
Structured support, psychotherapy, psychopharmacology	Decreases isolation/alienation
	Allows expression of feelings
	Treats concurrent depression, anxiety
	May reduce somatic expression of tension, anxiety, depression

TABLE 5-3. SPECIALIZED COGNITIVE-BEHAVIORAL INTERVENTIONS

Imagery/Hypnosis

Imagery is one of the most easily accepted, most useful noninvasive methods for managing pain. An increasing number of patients and physicians are familiar with relaxation and imagery techniques, leading to its growing use with cancer pain patients (53). A recent meta-analysis reported that hypnosis for pain has a moderate-to-large effect size with 75% of lab and clinical participants receiving substantial analgesia (39). Thus hypnosis and imagery strategies repeatedly have demonstrated the greatest effect size of all cognitive-behavioral strategies tested for efficacy in pain control (38,54). Although relaxation is not essential for imagery or hypnosis, these methods usually begin with relaxation as a way for patients to “tune in” to their bodies and begin to become more aware of internal sensations as preparation for changing these sensations. Progressive muscle relaxation can be provided either by focusing on deep breathing and relaxing muscles from head to toe or by moving through the body and physically tensing and relaxing each muscle in turn (55,56). Learning to recognize the physical sensations of tension and relaxation in the various parts of the body can be helpful to patients so that they may notice tension when it occurs and relax muscles. Once patients understand relaxation and deep breathing, imagery moves to exploring places and events where they have felt comfortable, healthy, strong, and capable. This is usually referred to as *pleasant place* imagery. Nearly everyone enjoys and responds to these positive images, which provide patients with an opportunity to turn their focus away from their pain and strain for a time. In turn, their enjoyment of the experience enhances the likelihood they will continue to use these methods. Imagining a pleasant place provides an image which is incompatible with the experience of pain. Neumann et al. (57) demonstrated that training in pain-incompatible imagery significantly increased pain tolerance, while also decreasing psychophysiological pain reaction.

Often, clinicians provide an audiotape of a session for patients and ask them to practice between sessions so that they learn to use these skills on their own, whenever needed. We have found, as have others (33), that few patients benefit from just buying or being given an audiotape with imagery. Most people need the connection with a person who understands their unique circumstances and can help them adapt imagery to their preferences and needs. Tapes alone can bias patients against use of imagery, as we often hear in, “I tried that. It didn't work.” Treatment needs to be tailored to an individual's needs and preferences for optimal effectiveness (58).

When possible, we incorporate suggestions for analgesia in the painful area (59). Sensory transformation involving the use of images that transform the pain, such as seeing the pain as an object and watching as it changes color and shape, moves to a distant location, or decreases in intensity, can be very effective for brief or persistent pain (15,59,60 and 61). Our clinical experience indicates that pleasant-place imagery is effective as a distraction from discomfort, but to extend pain relief in the absence of the clinician, specific analgesic suggestions are needed. To assist patients in applying these skills on their own, we teach them the steps for using

imagery and provide suggestions for how easy and automatic imagery and increased comfort can be. For the purposes of pain management, research does not yet allow us to clearly distinguish effects of hypnosis from those of relaxation and imagery. Because of the negative connotations of hypnosis for some patients, we usually use the term *relaxation with imagery* unless a patient would benefit from the perceived magic of the term *hypnosis* (62).

When in-depth imagery is not possible because the patient is not interested or does not have the needed attention span, brief images or having the patient tell about their favorite experience or place can still provide a “time out” from pain and illness. When we begin imagery training, hypnosis or imagery itself may last for 20–30 minutes. As patients become familiar with the experience and as they are more ill, sessions may be as brief as 10 minutes.

Reframing

Just as the messages we give to patients are powerful, so are the messages patients give to themselves. Using this awareness, along with providing information and education, we help patients prepare “I can cope” statements to use in the face of major stressors. For patients with continuous pain or who are giving themselves negative messages, we teach them to do their own reframing. Reframing involves teaching patients to turn negative, unhelpful self-talk into neutral or more positive self-statements.

We prepare these statements by first exploring the messages a person is naturally giving him or herself. Many patients initially deny having any helpless or self-defeating thoughts. With an accepting approach, exploration, and some provision of examples from other patients, most people acknowledge specific fears or concerns that sometimes enter their minds about what might go wrong. Patients then develop alternative phrases to remind themselves of methods of pain relief where they have control such as, “This pain is really bothering me. What can I do right now?” With cognitive-behavioral skills training, patients will then learn to act on the added thought of, “The doctor said I should take another pain pill when the pain increases. I'll do that and then do some breathing and imagery until the pill starts to work. If it doesn't get better I can always call the doctor and he/she will find a better treatment.” It is important to emphasize that this approach is most effective when it is individualized. Specific self-statements and reframes must be adapted by, and developed with, each patient.

In discussing any cognitive modifications such as this with patients and families, it is essential to assure them that these messages alone will neither cure them nor kill them. They need not struggle to maintain only the “right” or only positive thoughts. Fears and helpless thoughts are normal and should be understood and tolerated as normal. More emotional and health damage is done by suppressing real feelings and thoughts than by expressing negative ones. At the same time, we encourage patients to use these thoughts to help them identify when they need more information or when they need reassurance from someone else whose knowledge or support they value.

In addition to working out reframes with the patient, we teach patients to reframe for themselves. After teaching them to identify negative self-talk, times when they expect the worst, or situations that really bother them, we teach them to

1. Focus on what they have accomplished rather than on what remains to be done.
2. Find something positive that they will gain from the situation and focus on that: “I'm coming through this. This is hard but I've learned I'm stronger than I ever imagined.”
3. Focus on what they would do to help someone else in the same situation: “If this were happening to my close friend, what would I tell him or her?”
4. Focus on the temporary nature of what is difficult: “This is difficult, but I know this will not last forever. In a half hour, I'll feel better.”

Cognitive-Behavioral Skills Training, Including Imagery or Hypnosis

Although there has been considerable interest in the use of psychological interventions for cancer, few controlled clinical trials have examined the utility of these techniques for pain management in cancer patients (63). Those done with a target of chronic nonmalignant pain or cancer-related general distress (which often accompanies persistent pain) demonstrate success (64,65).

We have completed two prospective studies testing the efficacy of cognitive-behavioral skills training for pain related to high-dose treatment for cancer. In both randomized controlled trials, we found that, when training was completed in two sessions before cancer treatment, patients learned the skills and used them to reduce severe pain even when opioids were used concurrently. In the first study we found that a hypnosis group reported significantly less pain without using more opioids than three comparison groups: a cognitive behavioral training with relaxation but without imagery, an attention control, or standard treatment (52). In a second clinical trial, we modified the groups, maintaining the hypnosis content but calling the intervention relaxation with imagery (15). This imagery alone was compared with three other groups again: (a) patient training in a cognitive-behavioral package that included reframing, distraction, self-affirmations, and relaxation with imagery; and (b) an active supportive therapy group that included education and reframing by the therapist; and (c) standard medical treatment. The imagery only and cognitive-behavioral groups reported significantly less pain than the standard care group. The supportive therapy group was not significantly different from either the standard medical treatment control group or the two intervention groups. We found that patients who received active therapeutic support had lower mean pain report, but the addition of either imagery or cognitive-behavioral skills training decreased pain further.

These results are similar to those reported by Spiegel and Bloom (14). In that study, breast cancer patients with progressive, disease-related pain were randomized to a standard-care control group, supportive group therapy, or supportive group therapy plus brief hypnosis for pain control. Groups continued for 1 year. The support and support plus hypnosis groups both reported lower pain and distress than the control group, with the hypnosis group reporting nonsignificantly lower pain than the support-only group.

A randomized controlled study conducted by Gaston-Johansson and colleagues (66) combined imagery with other cognitive-behavioral skills versus a standard care control group for breast cancer patients receiving autologous bone marrow transplant. The skills group reported reduced symptoms, particularly nausea and fatigue, but not pain.

Distraction

Similar to the quick, clinician-assisted distraction strategy previously described, distraction skills taught to patients teach them to focus attention away from their discomfort on their own. Distraction is something many of us do automatically when we have exhausted our abilities to solve problems or simply want a break from problems or preoccupations. Just getting through the day comfortably may be the greatest problem for patients suffering from cancer pain. In this case, focusing attention away from discomforts can be one of the more effective coping strategies. Individuals each have their own preferred distractions. We work with patients to identify which distractions work best for them and help them to plan when, where, and how they will use specific strategies.

Distraction is not the same as denial, which implies an inability to recognize reality. Nor is it the same as avoidance, which implies an unwillingness or inability to cope with reality. Distraction involves a willingness to accept reality while actively engaging ourselves in a positive portion of it.

Some distractions involve focusing on thoughts or *mental activity*. This can include self-statements, prayers, reading, listening to someone read, or listening to music. Focusing on pleasant images is another example. Other distractions focus on *active behaviors* such as working on a hobby, playing a game, or using deep breathing or relaxation. One of the most effective distractions reported by patients involves simply spending time with and talking with family and friends. Often the best way to focus attention away from discomfort is to create more pleasant or neutral sensations. Massage and exercise, such as walking, are commonly used. Regardless of the distraction, these types of activities provide a sense of achievement that reminds patients of their control over their own experience, but also recognizes that some problems cannot be “solved.”

Structured Support and Psychological or Psychiatric Referral

Support is one of the essential needs of cancer patients and family members. Although women are particularly likely to seek out emotional support, men are often more reluctant to use support. As a generalization, men are more likely to focus on problem-solving types of support provision. Including education as a part of support efforts can be an effective inducement for men who otherwise might resist support groups or individual support.

The value of support is being increasingly recognized in numerous studies examining the relationship of social support to physical and emotional well-being. A now classic group of research studies demonstrates that cancer patients who receive active psychological support, with or without skills training, from groups or individuals, report less pain and live longer (67,68). The expression of feelings and the sharing of experiences involved in supportive interaction may help patients to participate more fully in medical treatment. Researchers are exploring whether these support interventions have effects on survival and function through adherence to treatment, improved treatment through education, improved health-related behaviors, or neuroendocrine or immunologic effects that enhance survival.

Pain is among the significant contributors to emotional distress for cancer patients and vice versa (11,69,70,71 and 72). Pain intensity is related to negative cognitions, anxiety, and depression (69). Over time, unrelieved pain engenders feelings of helplessness and hopelessness. Helplessness or hopelessness leads to depression.

Depression needs to be treated concurrent with pain whether the depressed thoughts or actions seem related to unrelieved pain. It is most rare that depression resolves immediately on relieving pain. At the same time, treatment for pain should never wait for a test of depression or anxiety treatment. No data indicate that depression or anxiety cause physical pain in cancer patients.

Some patients develop or begin cancer treatment with phobias or panic that disrupts treatment and greatly reduces their ability to tolerate pain. Fortunately, these phobias and panic can be treated very effectively with desensitization strategies that use imagery and gradual introduction of the feared event to reduce anxiety. This treatment can make the difference between a patient's ability to proceed with medical treatment that may include discomfort or canceling all further disease-related care. If a patient seems particularly anxious, does not make repeated appointments either in a specific location or for a particular procedure but is otherwise responsible, or if a family member or patient reports fear to a health care provider, the patient should be evaluated for phobia or panic. Relatively small fears to those of us without them, such as needle phobia, elevator phobia, claustrophobia, or another procedure fear, can entirely prevent a patient from continuing lifesaving treatment.

When to Use Nonpharmacologic Methods

We are more likely to prevent difficult symptom management problems if we begin using nonpharmacologic strategies before pharmacological treatment fails. When pain is mild or new, patients are most receptive and able to learn strategies to help increase their control over symptoms. Once pain is moderate or has become chronic, patients may benefit from imagery done by a therapist, but are less likely to learn new cognitive-behavioral skills for use on their own. Attention span, concentration, and energy are necessary for learning new coping skills; all of these things can be affected by disease and its treatment. When patients are sedated or confused from medical treatments or a disease, or when patients are exhausted and frustrated because all other attempts to manage pain have not worked, we have a very difficult time teaching cognitive techniques for relieving pain. Information and education are always useful, but again are best provided when the pain problem is in early, mild stages. Physical methods, such as massage, ice, or heat, can be introduced at any point.

Although we do not have strong data yet on which psychological methods of cancer pain control are best for which types of patients, clinical experience with patients experiencing pain is quite similar to reports of cancer patients who have other distressing cancer-related symptoms such as chemotherapy-related nausea and vomiting. We can use this knowledge to provide us with some general guidelines (Table 5-4). Very anxious patients or those who avoid unpleasant topics or expect physicians and nurses to be in control have difficulty learning cognitive coping skills. These patients also may do well with hypnosis. After anxiety has been reduced and patients are feeling more in control of their own symptoms, cognitive-behavioral skills training may be introduced.

Method	Who will benefit
Assessment language for communication about pain	All patients, but ideally early in treatment to optimize care as treatment progresses
Use of 0–10 scale	
Verbal descriptors of pain	
Education and/or information about medical treatments and myths	All patients, as early in pain treatment as possible
Brief cognitive strategies	
Distraction, storytelling, or brief imagery	Patients with painful procedures or relatively brief pains
Reframing or meaningful phrase to repeat	Patients feeling out of control or with distressed views of their pain
Brief expression of thoughts and feelings	Patients with beliefs or distress disrupting relief of pain
Physical and complementary methods	Patients interested in alternative medicine techniques integrated with medical care
Massage	
Ice and heat	Patients with a caregiver or nurse able to assist or with adequate health to provide for themselves
Music therapy	Patients with finances or insurance to cover costs and a willingness to experiment
Other methods with physical therapist, rehab specialist, or complementary methods training	
Specialized cognitive-behavioral methods	
Imagery, hypnosis	Patients able to focus attention, relatively alert, with some motivation
Reframing and cognitive-behavioral training	Patients with residual pain after optimal medical treatment
Desensitization	Patients with phobia or distress related to needed treatment or procedures
Structural support, psychotherapy or psychopharmacology evaluation	Patients with moderate to severe distress

TABLE 5-4. WHEN AND WITH WHOM TO USE NONPHARMACOLOGIC STRATEGIES

At the other extreme, for patients who cope actively and manage anxiety well, it may be hard to measure improvement with skill training, but these patients are the most eager for additional coping techniques and report them to be very effective. Patients with moderate anxiety and those who have not prepared any coping plans may benefit the most from cognitive-behavioral methods. These patients are often motivated to learn skills that help them to feel like participants in their care. They feel more in control of their physical reactions when they learn the skills, and they respond well to the additional support provided by the trainer.

Conclusions

The nonpharmacologic interventions that we have described provide the clinician with simple and effective tools to assist with the management of cancer pain. In addition, these interventions give patients more control over their pain and treatment without making them choose between pharmacological and nonpharmacologic interventions. Because they are based on communication with the patient, the majority of these strategies can be easily used within the context of routine medical visits with the patient.

All patients need, and all clinicians can provide

- Assessment that teaches the patient what the physician needs to know to prescribe the appropriate treatment
- Procedural, sensory, and time-frame information that normalizes the experience, creates nonthreatening expectations, makes the experience more predictable, and reminds the patient that the current situation won't last forever
- Education that facilitates patient and family participation by teaching about treating pain, addressing barriers to patients reporting pain or taking medication, and informing why and when to call the doctor's office
- Simple cognitive strategies that remind patients of what is going well and help them recognize that they are doing a good job coping with a difficult situation
- Brief imagery that reduces focus on pain or reduces intensity of pain
- Information on physical and other complementary methods such as massage, ice and heat, music, and other methods of active distraction or use of alternative sensations to counter pain messages
- Brief time for expression of worries, concerns, fears, or helpless feelings

With specialized training, clinicians can help patients significantly reduce pain with the use of advanced imagery or hypnosis, reframing skills, distraction, and structured support. Nonpharmacologic strategies can become part of the overall treatment plan, alongside pharmacological treatments, to assure patients maximum pain relief and optimal quality of life.

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APPENDIX 5-1

EXAMPLES OF PATIENT PAIN TOOLS FOR HOME AND CLINIC USE.

YOUR COMFORT IS OUR CONCERN

[a handout to be adapted to your site, for patients & families]
These topics can be put in a brochure describing specific services for pain or given to patients before any procedure, surgery, or beginning of new treatment.
Key elements: large type for vision impairment, target for sixth grade reading level.

When you receive health care with us, we want you to know a few things.

Pain is important to us. If you have pain:

1. Tell your doctor or nurse.
2. We will keep working with you to treat the pain until it is managed.
3. There is NO BENEFIT from suffering with pain. Untreated pain is unhealthy.

   REMEMBER:
   "use your energy to get stronger or to do what is important to you, not to fight the pain"
4. If your first treatment doesn't work, we have MANY other options. Strong medicines like morphine are often used for strong pain;

   ➪ ADDICTION is rarely a problem.
   If you have been a heavy drinker, have taken pain medication or other drugs often, tell your doctor or nurse so they can plan your care.

   ➪ Let us know if you have any concerns about taking pain medicines.
5. COMMUNICATION is essential:
   We depend on you to tell us how much pain you have.
   We cannot know if you do not tell us.

   ➪ Tell us about problems with pain or treatment.

   ➪ Bring a pain diary or checklist to your appointment to tell us how your treatment has worked since we last saw you.

Fill out this form and take it to your doctor when your pain or symptoms change.

Your Name: _____

Date: _____

Tell Your Doctor about Your Pain

1. How strong is your **pain**?
   - Mark a "**W**" on the **Pain Scale** below to show how strong your pain is at its **worst.**
   - Mark an "**M**" on the **Pain Scale** to show how strong your pain is **most of the time.**

0	1	2	3	4	5	6	7	8	9	10
No Pain			Mild		Moderate			Severe		Pain As Bad As Can Be

PAIN SCALE

2. Where is the pain? On the picture below, mark the areas where you feel pain.

3. What does the pain feel like?
   - ☐ Pressure, Heavy
   - ☐ Aching
   - ☐ Throbbing
   - ☐ Cramping
   - ☐ Hot, burning
   - ☐ Sharp
   - ☐ Itchy
   - ☐ Numb or Tingling

4. Does the pain make it harder for you to:
   - ☐ walk
   - ☐ sleep
   - ☐ sit
   - ☐ work at home or out of the house
   - ☐ enjoy life
   - ☐ eat
   - ☐ be active

5. When is the pain worse?
   - ☐ In the **morning**
   - ☐ During the **night**
   - ☐ Before my **next dose of medicine**
   - ☐ When I **move**
   - ☐ I **can't predict** when it will get worse

6. How long does the pain last?
   - ☐ A few **minutes** but less than an hour
   - ☐ An **hour** or more but not all day
   - ☐ The pain is the **same all the time**
   - ☐ I have some pain **all the time**, but sometimes it gets worse

7. What other problems are you having?
   - ☐ Constipation
   - ☐ Dry Mouth
   - ☐ Dizziness or Confusion
   - ☐ Other Symptoms_____
   - ☐ Sleepiness
   - ☐ Nausea or Vomiting
   - ☐ Change in Mood

STANDARD ORDERS FOR AMBULATORY PAIN PATIENTS
Example

Pain Plan for:____[NAME]_____ Date:_____

1. Medications to take:

Medication	What to take it for: How much to take:	When to take it:
Long-acting morphine 30 mg (pink pill)	**Pain** 1 pill to keep pain controlled	Breakfast, 3–4 PM, Bedtime (every 8 hours)
Short-acting morphine 10 mg (white pill)	**Pain Breakthrough** 1–2 pills if pain increases. Up to 6 pills a day.	When pain increase starts.
Laxative	**Prevent Constipation** 2 pills 2 times a day. Do not wait until you have constipation, take this each day you take pain pills.	Morning Bedtime
Metoclopramide	**Nausea or Vomiting** Take when nausea starts, 1 pill at a time, 30 minutes between pills	When needed, up to 4 pills a day

2. Medications to stop taking: [LIST]

3. ___(phone #)_____ _____(name of RN or MD to call)_____
Call this phone number immediately if you have:

- Problems getting medication (either your pharmacy does not have it or it costs more than you can pay)
- New pain, Change in pain, No Relief with pain treatment
- Nausea or Vomiting more than 1 day
- No Bowel movement for 3 days
- Difficulty waking up in daytime
- Other mental or physical change that makes it hard to take medication

4. Your next appointment with Dr._____ **is:**

DATE: _____

Bell: _____

LOCATION: _____

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6

PHYSIATRIC APPROACHES TO PAIN MANAGEMENT

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Rehabilitation has too often remained marginalized in the care of cancer patients. The perception that rehabilitation only offers meaningful benefit to patients capable of full community and vocational integration with unrestricted life spans is inaccurate and shortsighted. Although physiatry, or physical medicine and rehabilitation, initially emerged as a field dedicated to transitioning individuals stricken with anatomically and functionally disruptive injuries back to productive lives, the scope of the field has broadened considerably as medicine has increasingly altered the prognoses of many formerly fatal diseases. Integration of rehabilitation services in the care of patients with faradvanced pulmonary and cardiac disease has become standard. Sadly, similar services are rarely offered to cancer patients, even in the early stages of disease.

Physiatric strategies geared toward enhancing pain control can be loosely grouped into three categories: (a) nonpharmacological nociceptive modulation, (b) adaptive functional training to allow pain-free mobility and self-care, and (c) restoration or preservation of normal biomechanics. These categories are theoretically separate but highly interrelated in practical application. Similar interventions are used to realize the goals of each. It is helpful, however, to consider them individually in developing an integrated plan to control pain, enhance function, and preserve autonomy in a given cancer patient.

FORMULATION OF AN INTEGRATED PAIN MANAGEMENT PROGRAM

Rehabilitative strategies fail in the absence of effective pain control. Adequate pharmacological analgesia lays a foundation on which physiatry can begin the work of advancing patients from a state of static to dynamic pain control. Pain management services allow rehabilitation professionals to effect functional gains and realize therapeutic goals. In turn, information gleaned during attempts to mobilize patients permits refinement of the analgesic regimen. Successful pain control is never fully achieved until the patient moves. For example, formerly quiescent pain from osseous metastases may become intensely problematic during attempts to transfer and ambulate.

Rehabilitation comprises an essential component of an integrated pain management program able to provide both symptom control and autonomous function. Ideally, physiatric approaches are seamlessly combined with appropriate disease-modifying, pharmacologic, and interventional analgesic strategies. This chapter addresses the three general categories of physiatric interventions (nociceptive modulation, achievement of pain-free function, and restoration of normal biomechanics). Approaches common to each are outlined, with special attention paid to their efficacy and limitations in cancer.

NONPHARMACOLOGICAL NOCICEPTIVE MODULATION

The capacity of thermal, manual, and electrical modalities to alleviate pain has long been recognized by clinicians. The classical Hippocratic texts outline the use of heat and massage to enhance comfort and reduce the virulence of disease (1). Investigative efforts have revealed the tremendous complexity of the neuroanatomical apparatus subserving nociception. Despite a baffling array of neurotransmitters and interneuronal connections, physiologists are now able to explain longstanding clinical observations. This understanding has led to increasing support for the use of manual, thermal, and electrical modalities in conjunction with conventional analgesic therapies.

Massage

Massage is one of the oldest and most widely accepted forms of treatment. Today more than 75 types of massage are practiced. Some forms are ancient, dating back over thousands of years (2). There has been a considerable increase in the popularity of massage over past decades. Its use in the treatment of illness ranging from minor myalgias to dire systemic disease processes has become accepted. The physiological effects of massage have been credited with promoting healing, restoring function, and enhancing physical performance. Specifically, massage has been described as assisting with circulation and lymphatic drainage, enhancing the elastic and inelastic properties of connective tissue and muscle, fostering relaxation, counteracting edema, and alleviating muscle pain (3,4,5,6 and 7). Malignancy has been cited as a relative contraindication to massage in the past. The concern stems from the possibility that massage may accelerate dissemination of malignant cells by enhancing the flow of lymph and blood. Several facts illustrate the limitations in this line of reasoning. Firstly, aerobic exercise is a more potent stimulant of blood and lymph flow than massage (8). No association between aerobic exercise and the acceleration of malignant spread has even been suggested. Secondly, manual lymph drainage, a massage technique specifically designed to enhance the transport capacity of the lymphatic system, has been use extensively in the treatment of lymphedema (9). Despite documented acceleration of lymph transport, manual lymph drainage has never been reported to potentiate recurrence or dissemination of cancer cells.

Thermal Modalities

This part of the chapter focuses on thermal modalities in treatment of cancer-related pain. Thermal modalities have been used by physiatrists for many medical conditions associated with disabilities. Some of the best applications of thermal modalities have been described in the literature on stroke, traumatic brain injury, and degenerative neuromuscular disease. Thermal modalities commonly employed in rehabilitation medicine include topical heat and cold, hydrotherapy, heat lamps, ultrasound, diathermy, fluidotherapy, and paraffin baths. Each of these is discussed in the following section on modalities used to treat pain in cancer patients.

Therapeutic Heat

The following discussion is limited to local applications of heat and cold as they pertain to cancer pain management and symptom control. There are three primary modes of heat transfer: (a) conduction, which includes hot packs and paraffin baths; (b) convection, which includes fluidotherapy, hydrotherapy, and moist air; and (c) conversion, which includes radiant heat, laser, microwaves, short waves, and ultrasound. Superficial heating modalities are discussed initially and deep heating modalities subsequently in this section.

Hot Packs or Hydrocollator Packs

Topical heat treatments attempt to warm tissues to between 40° and 45°C. They are primarily used to increase the mobility of a joint or the extensibility of collagen tissue; decrease muscle spasm; assist in the resolution of inflammatory infiltrates, edema, or exudates; increase blood flow; and afford analgesia. Hot packs, also referred to as “hydrocollator” packs, are the best known conductive heating modality. These packs are available in various sizes and consist of canvas bags filled with silicon dioxide. This compound, when exposed to moisture, absorbs many times its own weight in fluid, thus acquiring the large heat capacity of water. Heat has been

used as a part of cancer therapy and rehabilitation but certain safeguards must be applied when it is used (10,11). When a patient has a malignancy in an area to be heated, heat generally should not be directly applied, as temperatures below those therapeutic for cancer may accelerate tumor growth (12). Along the same lines, the increase in heat can increase the likelihood of metastases resulting from the improved blood flow and vascularity. The advantages of hot packs are many, including low cost and long life; suitability for use at home as well as in the hospital; patient satisfaction; and ease of use.

Hydrotherapy

Whirlpool baths and Hubbard tanks are currently the most common forms of hydrotherapy. These units, which are used to agitate water, are safe and provide convective heating, massage, and gentle débridement. When using hydrotherapy, treatment goals should be joint mobilization, débridement, or wound therapy. Temperatures can be adjusted, making this safe for cancer pain modalities (13). Hydrotherapy tanks can be used to immerse the whole body; this is useful in a patient with a large surface area that needs to be treated, whereas superficial heat is used for local pain relief.

Paraffin Baths

Paraffin baths are used far less than hot packs or hydrotherapy. Nonetheless they continue to have a definite role in cancer pain management. The typical bath is a container filled with a mixture of mineral oil and paraffin maintained at a temperature of 54°C. Although this temperature is somewhat higher than water-based therapy, it is tolerated because the mixture has a low heat capacity and an insulating layer of wax builds up on the treated area (20). There are two types of paraffin treatments. One is the dip method, in which a patient repeatedly dips a joint or extremity into the bath, removing the joint between dips to allow the paraffin to solidify. The area is covered or wrapped with plastic for approximately 20 minutes. The paraffin is then stripped off and placed back into the bath.

The alternate technique is for the patient to use the continuous immersion method for the treated part for 20–30 minutes at a time. Heating with this approach ensures a more intense warming of the joint or extremity; this is tolerated because a layer of solid insulating paraffin forms on the skin (14,15). This modality is useful in an extremity that may have a contracture, such as a hemiparetic or plegic patient who has a contracture or spasticity from a primary brain tumor.

Radiant Heat/Heat Lamps

Heat lamps are inexpensive, versatile, and an easy way to warm superficial tissues. Ordinary incandescent light bulbs can produce large amounts of infrared energy, so special infrared sources, such as quartz, are seldom essential. Heating rates and temperatures are adjusted by distance between the lamp and the patient—the $1/r^2$ law (16). In a cancer population this type of modality is not readily used except for instances in which it would be advantageous for the skin to stay dry or for heat application without body contact. For heating purposes, the portions of the viable light from yellow to red and the near and far infrared are used. The temperature distribution is highest on the skin surface and drops off in deeper tissues.

Ultrasound

The therapeutic ultrasound machine consists of a generator that produces a high-frequency alternating current of approximately 0.8–1.0 MHz. This high-frequency electric current is then converted by a transducer into mechanical, i.e., acoustic, vibrations (15). The transducer is a crystal inserted between two electrodes. The conversion of the high-frequency alternating voltage into mechanical vibrations is accomplished by reversal of the piezoelectrical effect (17,18 and 19). The goal is to produce vigorous therapeutic effects in deep tissues. This is effectively done by allowing the therapeutic applicator to produce average ultrasonic intensities of 3–4 W per cm^2. The physics of ultrasound is defined as a form of acoustic vibration occurring at frequencies too high to be perceived by the human ear. Thus, frequencies less than 17,000 Hz are usually called sound, whereas those above this level are designated as ultrasound. Of interest, with the exception of the differences in frequency, the physics of ultrasound is no different than audible sound.

The therapeutic temperature distribution of ultrasound is such that relatively little heat is absorbed into the subcutaneous fat; not much more energy is converted into heat in the musculature. One-half of the intensity at the muscle surface is still available at a depth of approximately 3 cm. Most energy is converted into heat at the bone surface. This makes this type of modality unique among deep-heating modalities and ideal for pain relief at the bone interface, as it does not cause extreme temperature elevation in the superficial tissues. Short-wave and microwave diathermies do not possess the depth of penetration of ultrasound and have fallen out of practical use in the treatment of pain. These physical modalities may be helpful in the cancer patient with pain of muscular or bone origin; however, heat can increase local blood flow and may be contraindicated in the cancer patient whose pain is at the site of a tumor mass (19,20). This modality may be beneficial and may provide analgesia on an area of local muscle spasm.

Therapeutic Cold

Cold modalities are traditionally used for acute musculoskeletal trauma, including edema, hemorrhage, and analgesia. Other uses include pain, muscle spasm, spasticity, muscle reeducation (as an adjunct), and reduction of local and systemic metabolic activity (21,22). Cold treatments are limited to superficial agents, and although marked decreases in skin and subcutaneous tissue temperatures are possible, the cooling of deeper tissue is restricted to a few degrees. In the treatment of cancer, the modality of cold might be employed with a patient who had an acute hemorrhage to a joint or had tumor fever in which cold might be of therapeutic benefit. Therapeutic cold causes vasoconstriction; it can be used as a counterstimulant, tending to inhibit the projection of pain information in the central nervous system. It should be avoided in areas of the body that have been previously irradiated (19).

Electrical Stimulation

Electrical stimulation may have a counterstimulation effect; it is usually applied superficially for pain and can provide analgesia through transcutaneous electrical nerve stimulation. If the pain is myogenic or of muscle origin, electrical current may be employed to fatigue muscle spasm or relieve muscular strain or tightness (20,23).

FUNCTION-ENHANCING THERAPIES

Classically, rehabilitation focuses on reducing the level of disability and handicap associated with a particular impairment. For example, the severe lower extremity motor deficits associated with complete paraplegia can be mitigated through the prescription of an appropriate wheelchair, instruction in independent transfer techniques, and use of assistive devices for the performance of activities of daily living (ADLs). A similar clinical approach can be extremely effective in reducing the functional morbidity associated with cancer pain. Discrete functional impairments can be identified and alternative means devised for accomplishing affected tasks. The goals behind this clinical approach are twofold: Pain is reduced while patients' functional status is simultaneously enhanced. Strategies routinely employed toward this end are outlined in the following sections.

Compensatory Strategies

A fundamental rehabilitation approach involves instructing patients in compensatory strategies for mobility and the performance of ADLs. This intervention assumes that a particular task or activity associated with pain can be accomplished in an alternate, less painful manner. For example, a patient with a pathological femoral fracture would be taught how to transfer from a seated to a standing position using the arms and unaffected leg for weight bearing. By deconstructing tasks required for mobility and ADL performance into discrete steps, therapists can determine which step(s) in a task sequence are sources of pain. Alternative means of completing the affected steps can then be devised and taught to patients. This approach allows intact, painless physiological systems and adaptive equipment to substitute for impaired structures. Therapeutic exercise is often used to supplement this approach. A common example involves instructing a patient to use his or her “good” leg and a toe loop to raise a plegic or painful extremity into bed during a sit-to-supine transfer.

Compensatory strategies can be used to minimize tactile stimulation of structures rendered allodynic by malignant involvement of the nervous system. Osseous structures affected by bony metastases can be “deweighted” to various degrees contingent on the risk of fracture and the degree of pain engendered by their use. Cancer patients with vertebral compression fractures can be taught how to transfer without imposing painful flexion moments on affected portions of the spine. It is critical to determine the musculoskeletal integrity of the extremities that will be used to relieve painful structures. This is particularly important for patients whose cancers have a predilection for osseous spread.

Adaptive Equipment—Mobility

Many patients require adaptive devices to enhance their safety and autonomy while moving about the home or community. Ready access to such devices is essential if advancedcancer patients are to remain socially integrated within their communities. Too often patients' social spheres collapse once the pace of advancing disease accelerates. Adaptive equipment designed to augment mobility ranges from prefabricated single-point canes to complex motorized wheelchair systems. Hand-held assistive devices are generally variations on canes, crutches, and walkers. A variety of available devices are pictured in Figure 6-1. Canes and walkers can be adapted

to distribute weight bearing onto intact structures to minimize the risk of pathological fracture. This is particularly important for patients with extensive osseous disease, as in multiple myeloma. Handheld assistive devices can greatly benefit patients with sensory impairments. Tactile feedback transmitted through the device supplements deficits in sensory input related to pathology in the afferent neural pathways. Chemotherapy-induced neuropathy is a common source of sensory impairment.

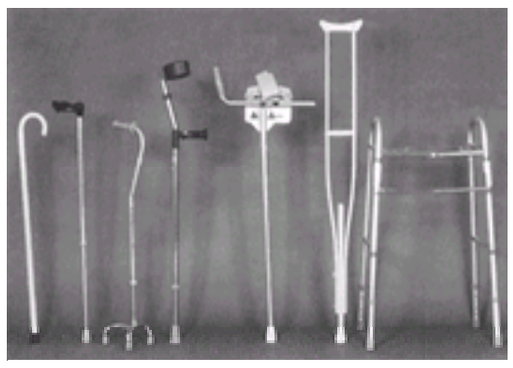

FIGURE 6-1. Common hand-held assistive devices to facilitate patient mobility.

Use of assistive devices enables deconditioned patients with limited exertional tolerance to participate in aerobic conditioning. Platform rolling walkers reduce the energy required for ambulation. As patients' stamina improves they are gradually transitioned to fewer and fewer supportive devices.

Adaptive Equipment— Wheelchairs and Scooters

Patients with severe deconditioning, paresis, osseous instability, or other sources of impaired mobility may require a wheelchair. Even when deficits are presumed transient, a wheelchair can sustain community integration and fragile social connections. Wheelchair tolerance and use are enhanced if an appropriate system is provided. There are many variables that can be specified to best serve the requirements and address the deficits of each patient. Arm-rests, for example, can be detachable to facilitate patient transfers. They are also available in “desk length,” enabling patients to maneuver close to desks and tables. Trough arm-rests can be used for patients requiring greater control of their upper extremities.

Seating systems are an element of wheelchair prescription with tremendous importance. If patients are uncomfortable, wheelchair use is inevitably reduced. Air cell, gel-filled, custom molded, and contoured foam cushions improve patient tolerance of sustained sitting and minimize skin breakdown. Chairs can be equipped with reclining backs, lateral trunk supports, and headrests to optimize patient comfort and stability. Cloth backing should not be used in the seating systems of patients at risk for vertebral compression fractures. Patients tend to slump forward in pronounced kyphosis, thereby increasing compressive forces on the anterior vertebral bodies.

Wheelchairs are available in manual and motorized configurations. Patients with sufficient strength to self-propel should be provided with handrims. These are placed slightly lateral to the wheel and are smaller in diameter. Cancer patients should not be provided with small diameter handrims. These require greater force per stroke. Knobby projections can be added to the handrims. These “lugs” assist patients with very poor grip related to distal arm weakness. If self-propulsion is not feasible, a motorized wheelchair is required. These chairs provide a high degree of independence, but are significantly more costly. Add-on power packs can be used to convert manual chairs to motorized power. These best serve individuals for whom a manual chair suffices most of the time.

Many advanced-cancer patients benefit from the use of motorized wheelchairs. Often the capacity to self-propel is lost as disease progresses. For this reason, anticipatory provision with a motorized chair is generally warranted. Wheelchair control can be adjusted to capitalize on muscle groups with sufficient power to manipulate a joy stick or switch. “Sip-and-puff “ drive control is available for patients with upper extremity paresis. Voice-controlled units remain experimental. Motorized scooters represent an excellent option for patients able to ambulate and transfer independently, but with insufficient endurance for extended ambulation.

Home and automobile adjustments must be considered when prescribing a wheelchair. Commercially purchased ramps are sufficient for many patients, requiring no home modification. If patients do not have access to a vehicle able to accommodate a motorized wheelchair or scooter, a collapsible manual chair equipped with an add-on power pack may represent the best option.

Adaptive Equipment— Activities of Daily Living

ADLs refer to the myriad functions required for personal grooming, hygiene, and feeding. Dependence for self-care has been shown to erode the quality of life of chronically ill patients (24,25). Minimizing each patient's requirement for external assistance is rehabilitation's most cherished goal. In the domain of self-care this is predominantly achieved through provision of appropriate assistive devices. Scoop dishes or plate guards (Fig. 6-2) can help patients with impaired motor control, or those who have the use of only one upper extremity to feed themselves. These devices allow patients to position food on their utensils independently. Nonskid mats, such as Dycem, can be helpful for patients with poor dexterity. Eating utensils can be easily adapted to the needs of each patient. Weight can be added for decreased stability or a bulbous handle can be used for reduced grip strength. A rocker knife (Fig. 6-3) can be used for impaired bilateral coordination. The knife is pushed down into food and rocked back and forth until the food is cut.

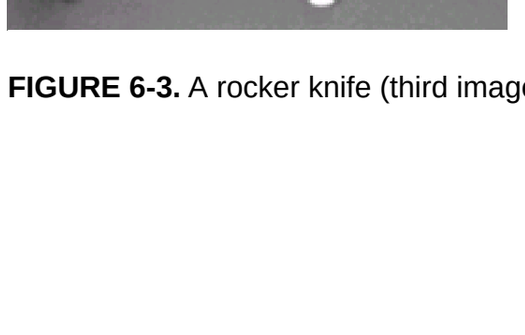

FIGURE 6-2. Scoop dishes to allow independent feeding for patients with impaired motor function.

FIGURE 6-3. A rocker knife (third image from the left) with other assistive devices for independent feeding.

Many devices are available to assist patients with independent dressing. When fine motor coordination is poor, fastening can be eased through the use of larger buttons, button aids, zipper pulls, elastic shoelaces, and Velcro. A button aid is a wire loop that hooks around a button and is then pulled through the hole. For patients lacking the mobility or dexterity to reach and grasp garments, reachers can retrieve items of clothing. A dressing stick (a long stick with a hook at the end) can help to pull clothing on. Stocking aids and long-handled shoehorns may help in a similar manner. A comparable array of assistive devices can be obtained to facilitate independent grooming.

Patients with impaired ADL performance should be referred for an occupational therapy evaluation. Most of the devices mentioned in this section can be obtained or fabricated by certified occupational therapists.

RESTORATION OF NORMAL BIOMECHANICAL ALIGNMENT

Cancer and its treatment have the capacity to adversely impact normal musculoskeletal physiology and biomechanics. Malignant lesions, particularly osseous metastases, can undermine the essential supporting structures of the musculoskeletal system. Tumors originating in or invading muscle tissue may cause severe weakness, requiring patients to recruit alternate, unaffected muscles in an effort to preserve their functional status. Patients with lower extremity sarcomas undergoing limb salvage procedures are an excellent example. Substantial portions of the knee and hip extensor muscles may be surgically resected. Continued ambulation requires recruitment of intact muscles and biomechanical adaptations. Anticancer treatments, including radiation therapy and chemotherapy, are known to cause muscle fibrosis and deconditioning, respectively. These effects may impact movement patterns when severe. Pain can also lead to significant biomechanical adaptations as patients attempt to avoid painful postures or movements. Ongoing biomechanical alterations are therefore an inescapable consequence of cancer and are experienced by virtually all patients.

Adaptive techniques become essential if patients are to remain mobile. Many biomechanical adaptations are adopted without conscious effort to avoid pain or to compensate for soft tissue contractures or muscle weakness. Unfortunately, the short-term benefit of such maneuvers may ultimately lead to long-term functional decompensation. For example, weight shifting and postural realignment used to relieve pressure from a compromised acetabular joint can eventually produce aberrant gait mechanics with associated pathology of the contralateral hip and bilateral sacroiliac joints. Another common clinical example involves head and neck cancer patients undergoing surgical neck dissection. These patients frequently develop spinal accessory nerve palsies with resulting weakness of the ipsilateral trapezius muscle. In an effort to continue using their affected upper extremities, patients recruit the remaining intact shoulder girdle muscles in a disorganized and deviant fashion. Although this maneuver may initially enhance shoulder abduction and forward flexion, rotator cuff and myofascial pathology eventually develop and may be a source of intense pain.

Three principal rehabilitative strategies permit restoration of normal alignment. Manipulative techniques abruptly return musculoskeletal structures to proper alignment through the controlled application of exogenous force. The therapeutic targets of such maneuvers are axial and appendicular joints. Manipulation is of limited benefit unless therapeutic exercise is concomitantly initiated. Therapeutic exercise, the second essential approach in biomechanical restoration, is frequently the initial and often the sole approach required. Muscles play a critical role in maintaining joint alignment and in modulating the body's many complex biomechanical rhythms (e.g., the gait cycle and scapulothoracic motion required for overhead reaching activities). Therefore, muscle weakness, contracture, and fatigability must be addressed if normal biomechanics are to be lastingly restored. Orthotics comprise the third strategy commonly used to align musculoskeletal structures for pain relief and functional enhancement. If weakness is severe, or if structures have been undermined to an irreparable degree, exogenous support (e.g., orthotics) can substitute and afford biomechanical normalcy. Often, as in the management of vertebral compression fractures, the use of orthotics is integrated with therapeutic exercise. For these patients the back extensor muscles can be strengthened while axial alignment is maintained through the use of an extension brace. Each of these three strategies (manipulation, exercise, and orthotics) is separately addressed in this section.

Manipulation or Manual Medicine

Manipulation has not been routinely offered to cancer patients despite the high prevalence of musculoskeletal dysfunction in this population. Many cancer patients develop aberrant biomechanical patterns as a result of pain, neuromuscular impairment, osseous instability, or radiation-induced soft tissue contractures (26). The adoption of such patterns is a normal response and necessary if patients are to remain mobile. However, the overuse of muscle groups in an unfamiliar repeated activity can lead eventually to spasm, malalignment, disproportionate muscle tone, and chronic pain. Manipulation provides a means of abruptly restoring normal biomechanical patterns and relief from musculoskeletal pain. Functional patterns can then be reinforced through physical therapy. Clearly the potential to harm cancer patients with irradiated tissue, bone metastases, and muscle weakness through the inappropriate application of exogenous force must be respected.

In the past, “manipulation” has traditionally been equated with high-velocity, thrusting techniques designed to maintain maximal, painless movement of the musculoskeletal system in postural balance (27). In actuality, a broad range of manipulative techniques has been developed. Manual approaches may involve stretching, passive soft tissue release, or strategic muscle contraction to produce counterstrain. The goal of manipulation or manual medicine is to restore optimal body mechanics and to improve motion in restricted areas. This is accomplished by treatments that attempt both to restore mechanical function of joints and to normalize altered reflex patterns in the muscles that control them (28). Manual medicine techniques are potentially useful for treatment of any musculoskeletal problem demonstrating a loss of functional range of motion. Complaints commonly treated with manual medicine techniques include “sciatica,” facet syndromes, mechanical cervical and lumbar pain, and piriformis syndrome.

Mobilization with impulse, or high-velocity, low-amplitude manipulation, is an approach widely equated with manual medicine. This technique is used to restore normal mobility to a discrete, dysfunctional segment (29). Similar effects can be achieved through the *articulatory technique*, which involves the combined use of leverage, patient ventilation, and a fulcrum to mobilize a joint limitation (30). This technique relies on repeated low-velocity, high-amplitude movements. *Muscle energy* is a gentle technique involving active muscle contraction by the patient against resistance supplied by the practitioner (31). Similar to the preceding approaches, the goal of muscle energy is to restore normal excursion to hypomobile segments. Strain and counterstrain is an additional well-tolerated technique designed to restore pain-free range of motion. It attempts to place a joint in its position of greatest comfort or ease by reducing exaggerated afferent proprioceptive activity.

Manual medicine techniques should only be used in patients having a reproducible musculoskeletal dysfunction. Each type of treatment technique has its own set of contraindications. Malignancy has been considered an absolute contraindication to high-velocity, low-amplitude thrusting maneuvers in the past. However, in experienced hands, symptomatic musculoskeletal structures documented as unaffected by malignancy can be safely manipulated. A cancer diagnosis warrants initial use of less forceful techniques. Muscle energy and strain and counterstrain measures should be applied first, in an effort to safely achieve clinical benefit. Caution must be taken in referring patients with severe osteoarthritis, genetic disorders with hypermobility, and metabolic bone disease.

Patients with mechanical pain or pain that can be reproduced through muscle recruitment in the absence of local tumor are candidates for manipulation. Osteopathic physicians are taught manipulation as an integral part of their medical education. Referral to an osteopath specializing in pain management and manual medicine is an appropriate initial step. Success depends largely on the skill and experience of the treating professional. Therefore, identification of a qualified individual is essential. Many physical therapists are trained in manual medicine. Physical therapy prescriptions should specify the desired treatment and precautions related to each patient's malignancy. For assistance in locating a qualified professional, the American Osteopathic Association can be contacted at (800) 621-1773 or http://www.aoa-net.org/.

Therapeutic Exercise

The prescription of exercise as a means of enhancing strength, coordination, stamina, and flexibility is the most important intervention offered by rehabilitation medicine. The recognition that our muscles and connective tissue respond predictably to imposed demands has spurred an elegant body of clinical research. Exercise should be prescribed at a clinically appropriate dose and frequency to optimize benefit and prevent injury. Too often the degree of infirmity found in advanced-cancer patients has resulted in their exclusion from exercise programs. Such patients can benefit significantly from conservative, incremental strengthening and conditioning programs despite their precarious health. This capacity has been demonstrated in other disease states characterized by comparable levels of morbidity (32,33).

When patients are hospitalized and medically stable, exercise can begin with gentle active and active-assisted twice-daily ranging of the extremities. Brief isometric muscle contractions can be performed in bed against gravity or with gravity eliminated. Isometric or static contractions are those involving no angular motion of the joint on which the exercising muscle acts. One brief isometric contraction per day was demonstrated to prevent loss of strength in bedridden rheumatoid arthritis patients (34).

Such an approach does not endanger the patient and minimizes deconditioning. As patients recover, exercise can be performed in a seated position isometrically or isotonically against resistance. An isotonic contraction is dynamic, with the tension on the muscle remaining constant throughout the contraction. More demanding resistive exercise, designed to build strength, can begin with resistance offered by a theraband. As patients improve, weighted ankle and wrist cuffs or free weights can be used. Resistive exercise has effectively improved strength in the elderly (35,36) and in patients with acquired immunodeficiency syndrome (37). Clinical investigation

with acquired immunodeficiency syndrome and aged patients suggests that the use of anabolic steroids augments the affect of exercise on cachectic muscles (38,39).

Aerobic conditioning differs from resistive exercise in its emphasis on continuous rhythmic contraction of large muscle groups. Jogging and cycling are examples. Conditioning programs have been demonstrated to benefit patients with end-stage chronic obstructive pulmonary disease (40) and end-stage congestive heart failure (41,42 and 43). Such programs do not significantly alter patients' cardiopulmonary status. However, the enhanced aerobic capacity of their muscles permits them to perform daily activities at a lower percentage of their maximal aerobic capacity. Progressive aerobic conditioning has been extensively integrated in standard care for cardiopulmonary patients, yet it is not routinely provided to cancer patients. Several investigations have demonstrated significant benefit with respect to fatigue, functional status, pain, and nausea when aerobic conditioning is administered concurrently with the delivery of adjuvant chemotherapy for breast cancer (44), or after high-dose chemotherapy during bone marrow transplantation (45).

Most of the research on exercise in the person with cancer has looked at the effect of aerobic exercise on functional capacity and quality of life. Presently, there is no consensus on an ideal type, frequency, intensity, duration, or mode of exercise. The trend of these studies indicates that there is a good cardiopulmonary response to interval training at 50–70% of the heart rate reserve or while working at an exertion of 11–14 on the 6–20 perceived rate of exertion scale (44,45). The intensity of the exercise program is dependent on baseline fitness levels, intensity of cancer treatment, and stage of cancer treatment. While undergoing treatment, most studies recommend decreasing the intensity to the lower end of the heart rate range. Once active therapy is over, the program should be progressed towards the higher end of the range. The intensity must also take into account daily lab values and patterns of fatigue associated with treatment. For example, fatigue seems to peak within the middle and end of the radiation cycle and the program should account for this pattern. Finally, duration and frequency should closely match the American College of Sports Medicine guidelines. It is recommended that patients exercise for a total of 20–30 minutes, 3–5 times per week. This recommendation must be applied carefully to patients with advanced cancer. Exercise may entail walking slowly for 5–10 minutes. The goal of a conditioning exercise program is to regularly stress the muscular aerobic apparatus to maintain or enhance physical capacity.

Exercise can also be used to enhance coordination, biomechanical balance, and flexibility. Motor learning and muscle recruitment are enhanced by appropriately prescribed exercise. Such neural factors, together with enhanced strength, account for improved biomechanics and coordination. Cancer patients whose functional decline arises from subtly impaired motor execution are excellent candidates for therapeutic exercise programs.

Orthotics

Orthotics are braces designed to alter articular mechanics when their integrity has been compromised by weak muscles, impaired sensation, bone metastases, or disrupted anatomical integrity. Orthotics may be used therapeutically to provide support, restore normal alignment, protect vulnerable structures, address soft tissue contractures, substitute for weak muscles, or maintain joints in positions of least pain. Orthotics are available prefabricated, “off the shelf.” Although such braces often suffice, patients may require more expensive custom orthoses for optimal benefit. Orthotics can be used to address pathology in virtually any articular structure. The use of these devices for cancer patients must be tempered by the overarching mandate of patient comfort. For example, a molded body jacket would provide maximal stability for a patient with diffuse vertebral metastases. However, the discomfort associated with wearing such devices, as well as the difficulty donning and doffing them, makes their use undesirable for many advanced-cancer patients. Similarly, Dynasplint produces orthotics designed to apply steady pressure on joints to elongate contracted soft tissue (Fig. 6-4). Although many cancer patients develop soft tissue contractures related to radiation therapy, the cost-benefit ratio of Dynasplint prescription must be carefully weighed before use in advanced-cancer patients.

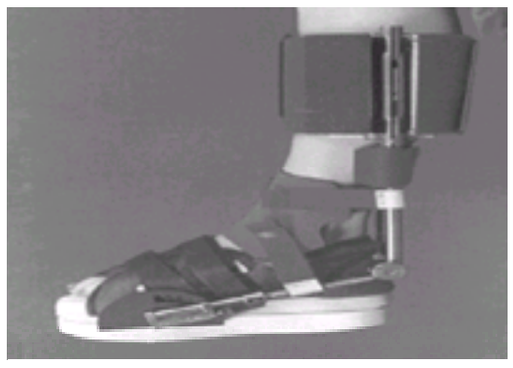

FIGURE 6-4. Dynamic splint, Dynasplint, for gentle stretching of soft tissue contractures.

Orthotics range from highly technical to remarkably simple. The orthotic most frequently prescribed by the author is an uncomplicated device called the universal cuff. This simple band encircles the metacarpal heads and has a small pocket into which eating utensils, brushes, pens, etc., can be inserted. For patients with distal upper extremity weakness related to neural compromise, this minimal device can restore the capacity for independent feeding, grooming, and keyboard manipulation. Additional commonly prescribed orthotics include the sternal-occipital mandibular immobilizer, molded ankle foot orthotic, and the Jewett brace. The sternal-occipital mandibular immobilizer (Fig. 6-5) deweights cervical vertebrae, thereby alleviating pain and instability in patients with cervical bony metastases. The molded ankle foot orthotic (Fig. 6-6) has been used extensively for patients with impaired ankle dorsiflexion due to tibialis anterior weakness. The Jewett brace (Fig. 6-7) is an anterior hyperextension orthotic designed to reduce compression of the anterior spinal elements. This device may control pain related to extensive metastatic involvement of the vertebral bodies. By limiting flexion, the device limits progressive vertebral collapse.

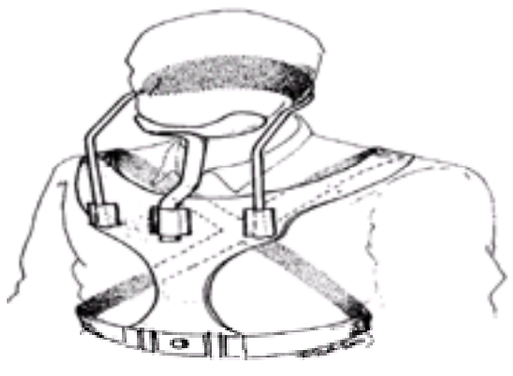

FIGURE 6-5. Sternal-occipital mandibular immobilizer orthosis.

FIGURE 6-6. Molded ankle foot orthotic.

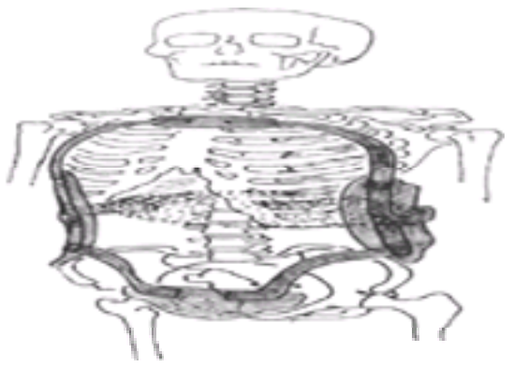

FIGURE 6-7. Jewett hyperextension orthotic.

Referral to an orthotist or physical medicine and rehabilitation specialist ensures that patients are provided appropriate orthoses. However, many rehabilitation professionals lack experience with cancer patients, particularly patients with advanced disease. It is important to communicate each patient's prognosis, goals of treatment, financial resources, and symptom-control issues to the rehabilitation professional. This gives patients the optimal chance of receiving the orthotic best suited to their unique requirements (Table 6-1).

TABLE 6-1. COMMON ORTHOSES USED FOR SPINAL STABILIZATION IN CANCER PATIENTS

Once an orthotic is in use, ongoing scrutiny of dermal integrity becomes a critical dimension of care. Cancer patients are rendered vulnerable to skin breakdown by a host of factors, several of which may collude in a given patient. Impaired dermal sensation, lymphedema, compromised nutritional status, immobility, diminished microarterial perfusion, and radiation-induced soft tissue change can render skin prone to breakdown. Dermal areas with prolonged redness after an orthotic has been doffed indicate the need for increased padding, pressure relief, or a return visit to the orthotist.

CONCLUSION

Rehabilitation offers the capacity to enhance pain control while preserving or restoring cancer patients' capacity to function independently. Physiatric evaluation can be of particular benefit to patients who experience pain with movement. Ideally, an integrated rehabilitative approach to pain management can be introduced concurrently with disease-modifying, pharmacologic, and interventional analgesic strategies. In the authors' experience, the combined use of modalities (manual, thermal, and electric) for nociceptive modulation; pragmatic task-oriented therapies for pain-free mobility and ADL performance; and strategies to restore biomechanical alignment optimizes both analgesia and functional autonomy. It is important to note that not all rehabilitation professionals are familiar with the fragility and unique requirements of cancer patients. For this reason it is critical that clinicians caring for cancer patients identify physiatrists; physical, occupational, and speech therapists; masseuses; and orthotists experienced in the care of patients with malignancy.

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7

NEUROSURGICAL INTERVENTIONAL APPROACHES TO PAIN

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SAMUEL J. HASSENBUSCH

A broad spectrum of neurosurgical operations and procedures have been used for the treatment and management of pain. The type of pain a patient is experiencing—cancerous or noncancerous, acute or chronic—and the quality of the pain depend on which of the various methods are used. For the purpose of organization, this chapter is subdivided into two sections. The first part is a brief discussion on the intracranial ablative procedures used in the treatment of pain. The second part of the chapter details the neurosurgical operations on the spinal cord for the management of pain. In addition to the various intracranial and spinal ablative procedures, a number of other surgical techniques have also been used in the treatment of pain. One of these techniques includes the use of electrical current—both deep brain as well as spinal cord stimulation. These are very broad topics that certainly deserve their own chapters for further discussion. For this reason, these two additional topics are not covered within the scope of this text.

Central ablative procedures remain important techniques in the neurosurgeon's management strategies against chronic pain. These are not entirely benign procedures, however, and often have potential risks to the patients. Furthermore, some of these intracranial ablative procedures are appropriate only after the failure of less invasive pain control measures.

MEDULLARY OR PONTINE TRACTOTOMY

Medullary or pontine spinothalamic tractotomy can be considered a treatment option for patients suffering from cancer-related pain that originates in the shoulder or cervical region (1). Specifically, one can consider this operation in patients affected with lung cancers that may produce Pancoast's syndrome or other squamous cancers that can affect the head and neck (2). There is a risk, however, of performing a medullary tractotomy—paralysis of the automatic phase of respiration. This can result in the development of sleep apnea. Furthermore, if the patient has a unilaterally paralyzed diaphragm due to lung cancer and this procedure is performed on the contralateral side, the patient may in fact die as the result of this procedure (3).

An open medullary or pontine tractotomy is usually performed under general anesthesia (Fig. 7-1). A posterior cervical midline incision is made, and a posterior fossa craniectomy and C-1 laminectomy are performed. The incision into the spinothalamic tract is made, with care as to not make the lesion above the obex. In this case, a spinothalamic tractotomy may damage the inferior cerebral peduncle and cause gait abnormalities.

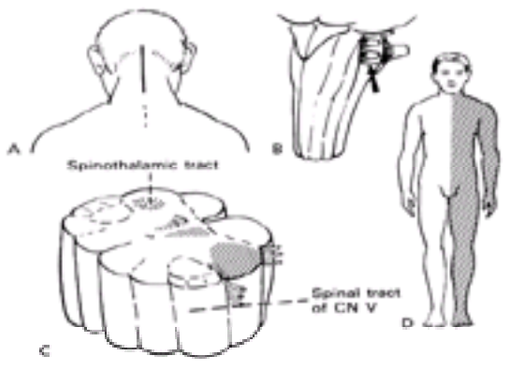

FIGURE 7-1. Medullary spinothalamic tractotomy. **A:** Site of skin incision. **B:** Dorsolateral view of medulla indicating site of incision in brainstem. **C:** Cross section of medulla indicating depth of incision into dorsolateral medulla. **D:** Extent of analgesia after right medullary spinothalamic tractotomy. CN, central nerve. (From Young R. Ablative brain operations for chronic pain. In: Loeser JD, ed. *Bonica's management of pain*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, with permission.)

These procedures also do not relieve the dysesthetic, burning pain that may often accompany malignancies. This is in part thought to be due to the fact that a large portion of the paleospinothalamic tract already branches off at the level where the surgical lesion is made. Consequently, these fibers are not interrupted with a tractotomy.

Past literature contains success rates between 80% and 90% for the relief of cancer pain (4,5). However, this is not a currently popular procedure for the treatment of pain. The reports in the literature make note of the fact that most individuals who did in fact undergo this procedure did not survive for longer than 6 months postoperatively (6). Furthermore, there is an overall complication rate of 14% with this procedure when used for the treatment of noncancerous pain (7). As a result, a number of therapeutic alternatives remain more appealing.

MEDULLARY TRIGEMINAL TRACTOTOMY

The medullary trigeminal tractotomy is a surgical procedure that is primarily performed for the management of facial pain. This procedure is somewhat advantageous to complete sectioning of the trigeminal nerve. It allows sparing of the sensation of proprioception and touch in the facial region, particularly the corneal reflex.

This procedure is usually performed under general anesthesia. The patient is placed in the prone position, and a posterior fossa and upper cervical exposure is performed. Once the dorsolateral sulcus is identified, as well as the obex, an incision is made into the dorsolateral medulla (Fig. 7-2).

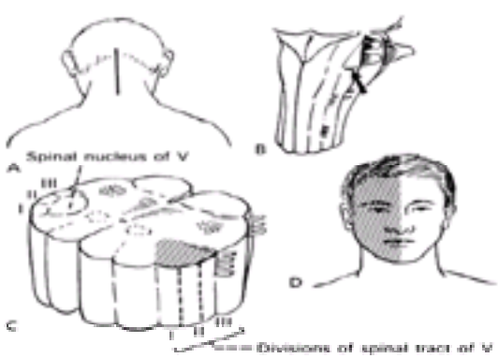

FIGURE 7-2. Medullary trigeminal tractotomy. **A:** Site of skin incision. **B:** Dorsolateral view of medulla indicating site of incision into brainstem. **C:** Cross section indicating depth of incision into dorsolateral medulla. **D:** Extent of analgesia after right medullary trigeminal tractotomy. (From Young R. Ablative brain operations for

chronic pain. In: Loeser JD, ed. *Bonica's management of pain*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, with permission.)

A stereotactic technique has also been described for the purpose of performing a tractotomy (8,9 and 10). This requires the patient to remain in the prone or sitting position and requires the neurosurgeon to perform this procedure via a smaller exposure. It has been used for the treatment of cancer pain, as well as for chronic, noncancerous pain conditions of the face—excluding anesthesia dolorosa.

MESENCEPHALOTOMY

The mesencephalon has long been thought of as a center for pain input from both the head and body (11,12). The primary indication for stereotactic mesencephalic tractotomy is cancer pain related to the head, neck, and upper extremities (13). Particularly, this procedure can be performed in individuals who may have unilateral diaphragmatic paralysis and in whom a high cervical cordotomy may be hazardous (13). In addition, conditions such as anesthesia dolorosa as well as postherpetic neuralgia may also respond to mesencephalotomy.

The procedure of stereotactic mesencephalotomy is performed in conjunction with stereotactic magnetic resonance imaging. This helps to better target where the lesion is to be performed. The ultimate target, however, is subject to debate. Some individuals believe that a lesion at the level of the superior colliculus results in up to 75% pain relief but causes a high percentage of ocular movement abnormalities (13). Lesions at the level of the inferior colliculus are less effective in pain control than those at the superior colliculus but have a significant reduction in possibility of ocular disturbances (14,15). In addition to the ocular disturbances that can occur with a stereotactic mesencephalotomy, dysesthesias as well as motor complications can occur.

THALAMOTOMY

Stereotactic thalamotomy remains a procedure that can be effective in patients with refractory pain (13). Specifically, thalamotomy can be used to treat cancers affecting the head and neck as well as tumors that may invade the upper brachial plexus and cause a Pancoast's syndrome (13,16).

This procedure is performed with the patient under local anesthesia, using stereotactic techniques. In addition, with the improvement in imaging, as well as with magnetic resonance imaging target localization, stereotactic thalamotomy is a relatively safe and accurate procedure. It may be a more appealing procedure for patients who may be at high risk for general anesthesia.

Other intracranial procedures that are noted within the literature include hypothalamotomy, hypophysectomy, precentral and postcentral gyrectomy, frontal lobe operations for pain, and cingulotomy. These procedures are used rather infrequently and are mentioned for reference (17).

This portion of the chapter focuses on the various neurosurgical operations carried out on the spinal cord for the relief of chronic or cancerous causing pain. The three major procedures discussed here include anterolateral cordotomy, myelotomy, and dorsal root entry zone (DREZ) lesions. These ablative spinal procedures serve as intermediate options between the intracranial–brainstem ablations and peripheral nerve lesions. The risks incurred with spinal procedures are generally lower than those associated with intracranial procedures. However, they have a more limited pattern of anatomical coverage. Peripheral denervations are technically easier to perform but often affect only a very limited anatomical area and have a higher chance of pain recurrence. The actual selection of an operation for a specific patient should be based on the type of pain (e.g., nociceptive, neuropathic, or visceral), the location of the pain, and the cause of the pain (e.g., cancer vs. noncancer).

Intraspinal ablative procedures, much like the previously described intracranial ablative procedures, are not first-line treatments for pain. They remain in a second tier of a long treatment continuum that includes (a) systemic treatments, such as various medications or physical therapy, (b) direct operations, such as spinal stabilization or surgical decompression, (c) thorough psychological evaluation and treatment as appropriate, and (d) chemotherapy and/or radiotherapy (for cancer patients).

ANTEROLATERAL CORDOTOMY

Anterolateral cordotomy is the surgical procedure by which the spinal anterolateral ascending system for the transmission of pain (spinothalamic tract) is interrupted for the relief of pain. A percutaneous and an open technique are options: The anatomical goal for each technique is the same, and results differ only with respect to the risks of each strategy and to long-term results. In many ways, it represents another example of an old procedure that has recently found increased use because of the percutaneous technique, especially with computed tomography (CT) guidance.

In 1910, Schuller first proposed the concept of relieving pain by sectioning the pain-conducting pathways in the anterolateral quadrant of the spinal cord (18). It was not until 2 years later, however, that Martin (19), at the urging of Spiller, performed the initial thoracic cordotomy in a patient with pain from a tuberculoma. Stookey was the first to report successful high cervical unilateral and bilateral cordotomy for severe pain (20). Foerster and Gagel reported similar unilateral procedures a year later (21).

The concept of a percutaneous stereotactic procedure was advanced by Mullan et al. to avoid or minimize the risks of an open procedure (22,23). Percutaneous methods could be accomplished under local anesthesia simply and easily and with a low morbidity rate in patients who otherwise might not be suitable for a major open operation (Fig. 7-3).

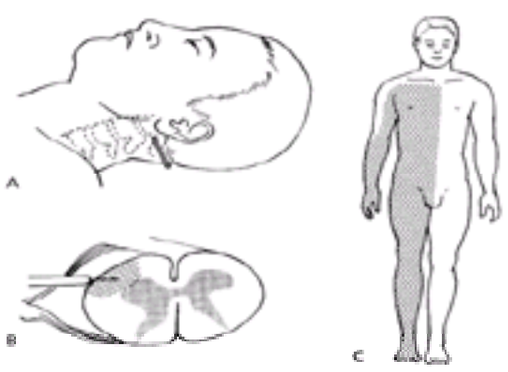

FIGURE 7-3. A: Site of percutaneous C-1–C-2 cordotomy. **B:** Lesion produced by percutaneous C-1–C-2 cordotomy. **C:**Extent of analgesia produced by left C-1–C-2 percutaneous cordotomy. (From Garber JE, Hassenbusch SJ. Neurosurgical operations on the spinal cord. In: Loeser JD, ed. *Bonica's management of pain*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, with permission.)

The initial method for percutaneous cordotomy first used a radiostrontium-tipped needle that was inserted into the spine at the C-1 to C-2 interspace laterally. This needle came to lie anterolaterally in the subarachnoid space adjacent to the ventral quadrant of the spinal cord. The next approach introduced a wire electrode into the parenchyma of the spinal cord so that anodal current could be used to create the lesion in the ventral quadrant. Rosomoff and associates in 1965 proposed a technique using a radiofrequency current to produce the lesion, which allowed for rapid and permanent lesion making (24). Electrophysiological monitoring of electrode position by electrical impedance and electrical stimulation were described by Gildenberg and associates and by Hitchcock and Tsukamoto and Tasker and Organ, respectively (25,26 and 27). The techniques have become standard with the use of myelography to confirm spinal cord and dentate ligament position (28). CT guidance has added another level of accuracy to this procedure (29). Two other approaches (low anterior cervical “through the disc” and occipital–C-1 dorsal cervical) have also been described but are not widely used (30,31).

Optimal candidates for this procedure should have unilateral severe pain not adequately treated by less invasive methods. With regard to neuropathic pain, cordotomy appears to be more effective in the treatment of intermittent shooting pain and evoked pain (i.e., allodynia and hyperpathia) rather than distressing dysesthesias, such as steady, burning, prickling, aching, or crawling (32). Tabetic or pseudotabetic pain, although it has a dysesthetic quality, seems to respond to cordotomy as well.

Anatomically, the procedure is indicated for pain in C-5 or lower dermatomes, preferably unilateral. It is almost entirely used for patients with pain from cancer, including those who previously could not be subjected to the major operation of laminectomy and spinothalamic section because of debilitation or a preterminal state. It is

increasingly rare to use cordotomy to treat painful conditions that are intractable and nonmalignant in nature, although some argument can be made for use in the treatment of nociceptive pain, albeit of noncancer origin (33). When bilateral cordotomy is required the contralateral procedure is performed as a second stage no less than 1 week after the first.

The major contraindication to either percutaneous or open surgical cordotomy is severe pulmonary dysfunction. A previous pneumonectomy is not an absolute contraindication, provided that remaining pulmonary function is satisfactory. The area of interest, the reticulospinal tract, is critical for automatic or unconscious breathing. Because of its proximity to the spinothalamic tract, this is somewhat of a concern when performing a cordotomy. Prior loss or significant decrease in this automatic breathing on the opposite side (e.g., from prior contralateral cordotomy or Pancoast's syndrome) can lead to a total loss of unconscious respiration (Ondine's curse).

Recently acquired neurological deficits, such as paresis or rectal or bladder disturbance, can be aggravated or recovery delayed by the superimposition of cordotomy. In this the case, the effect is usually temporary. Midline pain is a relative contraindication, even with bilateral cordotomy. General medical contraindications such as a severe bleeding diathesis, unstable cardiac function, and untreated severe systemic infection should also be taken into consideration before performing these procedures.

In the majority of series published in the literature, almost all cordotomies have been performed for pain from cancerous origin, often lung or gastrointestinal type cancers. Rarely, the procedure has been used in the treatment of lumbar radiculopathy or peripheral neuropathy (34).

The spinothalamic tract can be located in 95–99% of patients. However, the surgeon should not be hesitant to perform an early reoperation if appropriate analgesic levels are not obtained for technical reasons in the first cordotomy (33). “Adequate” levels of pain relief are found in as high as 95% of patients on discharge from the hospital. At last follow-up, however, the success rate can drop to 84% (33). Review of other published series suggests long-term success rates of 50–75%. Rosomoff and colleagues have shown that the satisfactory analgesia rates gradually drop over time since the operation: 84% at 3 months, 43% at 1–5 years, and then 37% at 5–10 years (34). It should be noted, however, that this refers to absolute pain relief. It is estimated that >50% of these patients felt they had received major help, could return to routine activities, and did not have problems of drug usage or distress severe enough to undergo repeat cordotomy.

Repeat cordotomies may be necessary in 10–20% of patients and, despite the prior cordotomy, can usually achieve levels of analgesia to acute testing pain. It appears that true pain relief, however, is captured in only approximately half of these patients undergoing a repeat cordotomy (33,34).

A comprehensive summary of complications from unilateral cordotomy indicates that, in general, the complication rate is low (33). The mortality rate can vary between 0.6% and 6.0%, almost always related to respiratory problems. Bowel incontinence and mild worsening of micturition can be seen in up to 2–10% of patients—both should be transient. Significant, permanent worsening of bladder function, however, can be seen in 2–10% of patients. Although information relative to sexual function is difficult to obtain, it appears that approximately 4% of males will note decreased sensation about the genitals on the analgesic side; true impotence appears to be very rare, even with bilateral cordotomies.

Although a postoperative Horner's syndrome is frequently seen (as often as 75% of patients), it is usually transient. Many patients will complain of transient neck pain, often described as burning or dysesthetic, from the area of the needle puncture. Transient hypotension can also be seen (2–8%).

Permanent weakness or ataxia, usually ipsilateral to the side of the cordotomy (2–10%), is a potential side effect. A mild or transient ipsilateral weakness/ataxia is reported in 3% to as many as 70% of patients. Contralateral limb weakness, presumably from lesioning too deep into the spinal cord, can also occur (1–6%).

Respiratory problems after unilateral cordotomy are rare and mild or transient (1–5% of patients). Severe respiratory failure can occur in 0.5–1.0% of patients but is more often seen as sleep-induced apnea (Ondine's curse) after bilateral cordotomies. The mechanism is related to an ascending system that contributes to the control of ventilation and is mediated through the upper cervical spinal cord (35). It is delayed in onset and can be predicted by testing the patient's response to breathing carbon dioxide (36). Ablation of the response, which is normally a two- to threefold increase in minute volume, predicts the appearance of the syndrome, but not all patients go on to apnea. The process is usually self-limiting, lasting a few days to 3 weeks.

Postcordotomy dysesthetic syndromes—burning distress throughout the entire area that was made analgesic—can occur in 1% to as many as 10% of patients. The mechanism of action is unknown. Dysesthesias in 16% are noted separately. These sensations (e.g., tingling, burning, prickling in the area of pathological implication) are not complications per se. They are uncomfortable feelings that were usually present preoperatively but were not conspicuous because of overriding pain. Once the pain had been ablated by the cordotomy, the dysesthesias became discernible and prominent, although it usually takes time to develop.

OPEN SURGICAL CORDOTOMY

Open surgical cordotomy has become largely of historical interest only (Fig. 7-4). However, the open technique might still be used in some rare circumstances such as in facilities in which percutaneous cordotomy equipment is not available or the surgeon performs the procedure so infrequently as to lose skill. When the patient is unable to tolerate any procedure while awake, a percutaneous cordotomy can be performed under general anesthesia in a manner similar to above except that, of course, sensory testing with 100-Hz stimulation cannot be performed. The indications for the open technique are the same as the percutaneous counterpart.

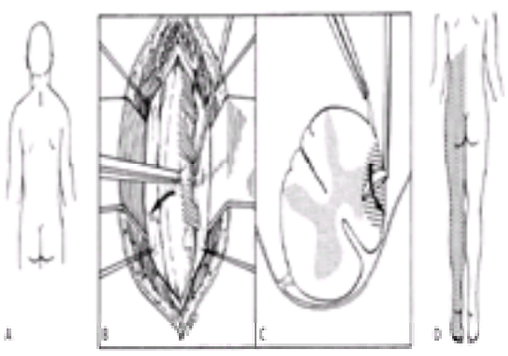

FIGURE 7-4. A: Site of open thoracic cordotomy. **B,C:** Method of performing open thoracic cordotomy. **B:** After T-1–T-2 laminectomy, the dura is opened and the dentate ligaments sectioned. The linea alba is grasped in a hemostat, and the spinal cord is rotated 45 degrees. **C:** A special cordotomy knife is used to section the anterolateral quadrant. **D:** Extent of analgesia on dorsal surface produced by right T-1–T-2 open cordotomy. (From Garber JE, Hassenbusch SJ. Neurosurgical operations on the spinal cord. In: Loeser JD, ed. *Bonica's management of pain*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, with permission.)

Following open cordotomy, immediate relief was reported in 70–90% of patients who had undergone unilateral procedures and in 40–78% of those with bilateral procedures. Mortality rates ranged from 3% for the unilateral procedure to 20% for bilateral procedures. Paresis and urinary complications were high (10–20%), especially after bilateral procedures. Respiratory complications comprised the most common cause of death (17). Postcordotomy dysesthetic syndromes can occur in 11% of patients. Open surgical cordotomy seems to be less effective and certainly has a higher risk of complication than the percutaneous techniques.

Percutaneous cordotomy is simpler and better tolerated than the open surgical technique. Because the anatomical and physiological bases for pain relief are the same for all cordotomies, true differences in long-term results might not be discernible. However, such advantages as the ease of performance and drastic reduction of risk and the additional advantages of repeatability ad infinitum, make percutaneous cordotomy the procedure of choice.

Percutaneous cordotomy is a valuable procedure for the treatment of severe pain syndromes, especially if located in one limb and nociceptive in quality. With the addition of CT guidance, the technique has become more facile. The risks of the procedure are significant but acceptable for this group of patients, especially those with limited expected survival times from cancer. The benefits, in terms of almost immediate pain relief and limited need for outpatient follow-up, are both cost effective and gratifying.

MYELOTOMY

Commissural myelotomy at the thoracolumbar level for the treatment of pain was first described by Armour in 1927 for a patient with tabetic abdominal pain (37).

Putnam (38) was apparently unaware of this report when he claimed to have performed the first myelotomy in 1934. Since then the popularity of this operation has waxed and waned. It seems quite logical that neurosurgeons would aim at producing bilateral pain relief with a single low-risk procedure that has little risk of damage to the important spinal axonal systems. Unfortunately, this apparently attractive operation has not been as effective as predicted on theoretical grounds. After the initial attempts on a few patients, commissural myelotomy was applied on a relatively large scale by French and German neurosurgeons in the 1940s and 1950s (39,40 and 41), subsequently becoming relatively obsolete for several years. At the end of the 1960s, Sourek (42,43 and 44) published encouraging results and once more aroused the interest of neurosurgeons in this technique. In the last 15 years the topic has recurred sporadically in the neurosurgical literature, with various results reported (45,46,47,48,49,50,51,52,53,54,55,56,57,58 and 59). Approximately 425 myelotomies have been reported in the neurosurgical literature.

The original aim of commissural myelotomy was to interrupt the decussating second-order spinothalamic fibers subserving pain perception on both sides of the body as they travel in the anterior commissure of the spinal cord. Theoretically, bilateral symmetrical analgesia should have been achieved, with pain relief restricted to the segments where sensation had been altered. The length of the myelotomy incision should have been proportional to the extent of pain. What was seen, however, even after extensive longitudinal splitting of the spinal cord over several centimeters, was that a girdle of analgesia was present in the expected area but that pain relief extended caudally into regions that had no demonstrable sensory changes. Hence, the role of the spinothalamic fibers in pain relief after myelotomy is not clear.

Various hypotheses have been proposed to explain this antalgic but not analgesic effect of myelotomy. Sourek (42,43 and 44) theorized that the spinal commissurotomy interrupts two systems that conduct pain information: the slowconducting anterolateral system and the fast-conducting mediodorsal system. The latter was believed to have a somatotopic arrangement and was contained in the medial portion of the posterior columns.

Sunder-Plassmann and Grunert (45) reported their experiences with 56 midline myelotomies and described only bilateral segmental analgesia appropriate to the level of the myelotomy. In contrast, Hitchcock (46,47) and Schvarcz (48,59) carried out cervical stereotaxic myelotomies and reported extensive areas of pain relief without sensory changes. They thought that their procedure specifically interrupts an extralemniscal centrospinal multisynaptic pathway, with Schvarcz referring to *extralemniscal tractotomy*.

From an anatomical standpoint, Kerr and Lippman reported that the projections to the periaqueductal gray matter seen in cordotomy are topographically different from those seen in myelotomy (60). The gray matter around the central canal has been shown to have anatomical connections to brainstem areas involved in nociception (61). In patients who have had an open myelotomy, disorders attributable to damage to the posterior columns are frequently observed for several weeks after surgery.

The two basic strategies for midline myelotomy are the following: open, requiring a laminectomy, opening of the dura, and making a lesion under direct vision; and closed, making a lesion through a needle that has been passed through the skin, between adjacent laminae, and into the spinal cord (Fig. 7-5).

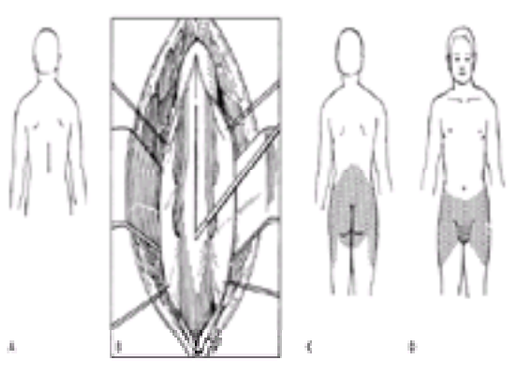

FIGURE 7-5. A: Site of thoracolumbar midline myelotomy. **B:** Method of performing midline myelotomy in thoracolumbar region. After a laminectomy of T-9–L-1, the dura is opened and the dorsal midline of the spinal cord identified. A microknife is used to make a midline incision to the ventral pial surface. **C** and D: Extent of analgesia produced by thoracolumbar midline myelotomy. (From Garber JE, Hassenbusch SJ. Neurosurgical operations on the spinal cord. In: Loeser JD, ed. *Bonica's management of pain*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, with permission.)

Open myelotomy is a major surgical procedure that should be considered with caution. Patients in poor condition who have a short life expectancy are not often suitable. On the other hand, even the most extensive myelotomies have not guaranteed long-lasting pain relief. A CT-guided technique has also been described in the creation of lesions in the same area (62).

Percutaneous myelotomy is described by only four surgeons; the procedure has probably been performed in approximately 150 patients, although pain relief in large regions of the body has been reported in as many as 79% of patients with cancer. Hitchcock (46,47), Schvarcz (48), and Gildenberg and Hirshberg (49) described making a lesion at C-1, and Sourek (42,43 and 44) made lesions both at C-1 and at T-8 to T-10. Coagulation of the high spinal central gray matter produces dramatic changes in sensation and pain relief over variable but widespread regions of the trunk and extremities. In this technique, only a single lesion is made in the center of the spinal cord at a segment just above the highest level of the painful areas. A single lesion is made at the thoracolumbar junction of the spinal cord (so-called *punctate midline myelotomy*) for the most common use of this procedure—pelvic visceral pain from rectal or uterine cancer (63). Follow-up times and areas of sensory loss have been variable, and the duration of pain relief is not clear.

Despite the well-documented shortcomings, there are certainly some rewarding clinical results. These come in cancer patients with pain in the pelvis, perineum, and/or both lower extremities. Good pain relief without significant analgesia is also occasionally seen (64). In combined series, total relief of pain or total cessation of analgesics was initially reported in 92% of 175 patients, most of whom had cancer pain. This rate, however, dropped to 59% at last follow-up or death in the cancer pain patients. There has been great variance in these results, however, between different series, possibly because of differences in technique, especially the depth of the sectioning.

Wertheimer and Lecuire (39), who applied myelotomy on a large scale nearly 40 years ago, initially stated that myelotomy provided satisfactory pain relief in most patients with bilateral pain in the lower half of the body. The same clinical material was subsequently reanalyzed by Dargent and colleagues (40), who concluded that myelotomy was effective only for the management of vaginal and visceral pain, whereas rectal pain and lower limb pain were not significantly influenced. Later, Sourek (42,43 and 44) and Broager (50) reported good results for the relief of lower limb pain, whereas Cook and Kawakami (51) and Lippert and associates (52) did not succeed in relieving lower limb or spinal pain. As for the pain located in the upper part of the body, Lembcke (41) and Cook and Kawakami (51) reported satisfactory results, whereas Sourek's (42,43 and 44) experience was disappointing.

With stereotaxic cervical procedures, Hitchcock (46,47) and Schvarcz (48) succeeded in most patients irrespective of the location of pain. Between these two series, 100 patients were treated. Follow-up until death or for up to 5 years indicated that approximately 70% of patients had satisfactory pain relief. Papo and Luongo (53), however, obtained only short-lasting relief with a cervical procedure (superficial splitting and deep coagulation) regardless of the type and location of pain, which always recurred in patients who survived longer than 2–3 months.

Sunder-Plassmann and Grunert (45) claimed that 91% of their patients were pain-free after midline myelotomy; 26% remained pain-free until their deaths or for the duration of follow-up, which lasted up to 4 years. Others believe that late pain recurrence as a result of a falling sensory level is rare (65). Myelotomy is a procedure confined to selected patients (66). All the published series have contained small numbers of patients.

Complications have been reported in 5–10% of the reported cases. Most surgeons agree that the typical open longitudinal midline myelotomy produces a temporary loss of pain and temperature sensation in a girdle area that corresponds to the region of the cord incision. How long this unexplained sensory loss persists is unclear. Postoperative mortality has been low (0–3%) in most recent series. Rarely, a dysesthetic or radicular pain of mild severity might occur at the top end of the area of pain relief (65). Other side effects include hyperesthesia, diminished proprioception, paresis or incoordination of gait, and motor and sphincter disturbances (64).

Although myelotomy remains a useful procedure, caution should be exercised with regard to recommending myelotomy as the initial procedure for the relief of cancer pain. This procedure can be useful for the relief of bilateral pelvic and perineal pain because the other surgical alternative is bilateral cordotomy, which carries increased risk of bladder dysfunction. Epidural and intrathecal narcotics have unquestionably greatly reduced the numbers of patients who need ablative surgery for cancer pain. For the management of noncancer pain, open myelotomy is difficult to accept. So few surgeons have reported on C-1 radiofrequency myelotomy that it is impossible to adequately evaluate this variant, which can have a different anatomical substrate from the low thoracic myelotomy. Using the present understanding of the anatomy and physiology of mesial spinal cord systems, myelotomy techniques can be chosen but should be coupled with objective assessments of side effects and effects on different aspects of the pain (67). Present data strongly suggest that this is an effective procedure, albeit for a limited subset of cancer patients with

intractable pain that is either bilateral or midline, especially located in the pelvis.

DORSAL ROOT ENTRY ZONE LESIONS

The DREZ operation entails making a series of lesions aimed at the substantia gelatinosa Rolandi and the surrounding fiber tracts. This operation was conceived and first used by Nashold and coworkers (68) in 1976 in a patient with severe pain secondary to brachial plexus avulsion. That patient has been reported to be free of pain ever since. By 1989 the Nashold group had done a total of 550 operations for various conditions (personal communication to Bonica, 1989). Almost 500 additional operations have been reported by other authors. Although Nashold and associates have the most extensive experience with this operation, many other neurosurgeons are performing this ablative procedure. The data published to date permit us to make some inferences regarding its efficacy.

This operation involves the destruction of dorsal horn neurons and perhaps of the axons traveling in juxtaposition to the gray matter, particularly those segments that correspond to the patient's reported area of pain. The detailed anatomy of the human dorsal horn is not discussed in this chapter. Rather, this chapter contains only a brief anatomical review relevant to this operation. The dorsal horn can be segmented on a cytoarchitectural basis into six laminae (Rexed's laminae). The five most superficial are clearly involved in the transmission of nociceptive information from the periphery and can play an essential role in some deafferentation or central pain states.

Not only are the synaptic connections from peripheral nociceptors localized in laminae I–V, but also studies have demonstrated major concentrations of opiate receptors, substance P, and other biologically active peptides in these regions. Indeed, many believe that the “gate,” as described by Wall and Melzack (69), resides in this region of the spinal cord. The combination of classic neurophysiology and modern pharmacology points to this region as being critical in the processing of sensory information. In 1967, Loeser and Ward (70) reported that neurons in the dorsal horn become hyperactive when deafferentated. Nashold and coworkers (68) subsequently designed an operation to destroy the dorsal horn in patients with deafferentating lesions and severe pain. Since initial successes have led to increasing use of this procedure, it has been almost exclusively used for pain states characterized by an injury to the nervous system referred to in this book as *deafferentation pain* and thought to have a peripheral-central pain mechanism; others have used the term *central pain*.

Few, if any, traditional surgical procedures have a significant chance of alleviating the pain that follows deafferentation (71). Certainly, rhizotomy, cordotomy, myelotomy, or sympathectomy is unlikely to produce long-term pain relief. DREZ lesions appear to be remarkably effective in brachial plexus avulsion and are reasonably effective for the relief of postparaplegic pain, postamputation pain, and postherpetic neuralgia and for a small number of miscellaneous neuropathies and myelopathies.

Brachial plexus avulsion, other brachial plexus destructive lesions, sacral root avulsion, and postparaplegic pain are diagnoses that have been considered as most appropriate for treatment by DREZ lesions. The procedure has also been used, although with a lower success rate, in the treatment of phantom limb pain, stump pain, postthoracotomy pain, postherpetic neuralgia, peripheral mononeuropathy, spinal cord tumor, multiple sclerosis, causalgia, and postrhizotomy pain. Specific predictive factors to indicate a favorable outcome are being developed.

The indications for consideration of DREZ lesions as a mechanism for the treatment of chronic pain include an established diagnosis and failure of medical-pharmacological management. In addition, it is important the patient has an understanding of alternative strategies, risks, and potential benefits. As previously mentioned, the diagnoses listed above are those that have thus far been considered to be appropriate for DREZ lesions. The number of patients treated, however, is currently limited in some of these diagnostic groups.

Contraindications relate to the patient's general health and ability to withstand a major surgical procedure, including such factors as infection, resistance to wound healing, blood and coagulation problems, and poor cardiopulmonary status. Patients who have a significant emotional component to their pain are rarely good surgical candidates, although the ravages of chronic pain can alter patients' judgment and emotions.

DREZ lesions are performed under general anesthesia and require a laminectomy over each segment to be lesioned. For brachial plexus avulsion involving C-5 to T-1 dorsal roots, it is necessary to do a C-4 to T-1 laminectomy (Fig. 7-6).

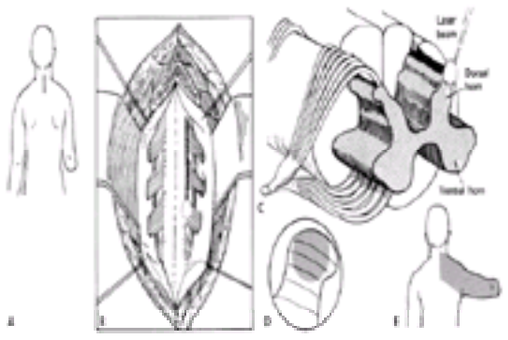

FIGURE 7-6. A: Site of C-5–T-1 dorsal root entry zone (DREZ) lesions. **B,C:** Production of DREZ lesion using carbon dioxide laser. **B:** After a laminectomy of T-1, the dura is opened, and the dorsolateral sulcus is identified. The pial vessels are coagulated and a continuous lesion made in the dorsolateral sulcus to destroy the DREZ. **C:** After the laser is used, a microprobe is inserted into the dorsal horn to verify its destruction. **D:** Extent of lesion in dorsal horn. **E:** Analgesia produced by right C-5–T-1 DREZ lesions. (From Garber JE, Hassenbusch SJ. Neurosurgical operations on the spinal cord. In: Loeser JD, ed. *Bonica's management of pain*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001, with permission.)

The postoperative course is usually benign; many patients have transient dorsal column or pyramidal tract dysfunction, but few have permanent deficits. It is presently unclear which method of destroying the dorsal horn is safest and most effective.

A major concern with regard to the placement of DREZ lesions is proper localization for placement of these lesions. The dorsolateral sulcus is varyingly discernible; when the dorsal roots have been avulsed, the dorsolateral region can be densely adherent to the arachnoid or to the dura. The dorsal horn is obliquely oriented and the electrode, knife, or laser beam must be angled or the spinal cord rotated to create the desired lesion and avoid damage to the pyramidal tract or the dorsal column. When roots have been avulsed or the spinal cord damaged, it is helpful to expose the levels rostral and, when feasible, caudal to the proposed operative area so that normal dorsal roots can be visualized and the dorsolateral sulcus can be identified. Evoked potentials can also be used to localize the superficial tracts in the spinal cord and assist in the placement of lesions (72).

The most common and most successful application of DREZ lesions is for the relief of the pain of brachial plexus avulsion. This traumatic disaster is most common in young men who ride motorcycles. Nashold's first patient suffered from this injury. An overall 83% success rate has been reported, with many follow-ups of longer than 5 years (68,73,74,75,76,77,78,79,80,81,82,83 and 84). A few patients with sacral root avulsions have been included in these series. No other diagnosis has as high a likelihood of success, and no other operation is as likely to relieve this type of deafferentation pain.

Postparaplegic and postquadriplegic pain is relieved by DREZ lesions (73,75,76,78,84,85 and 86). The long-term success rate is 54%, but the duration of follow-up has been variable. Some of the reported patients had drainage of posttraumatic syringomyelia at the same time; it is unclear if DREZ lesions alone are responsible for their pain relief. It is puzzling that distal spinal cordectomy does not often relieve this type of pain but that DREZ lesions are sometimes effective. It should be recognized that this is not radicular pain, nor is it the pain associated with osseous instability that can occur with traumatic injury to the vertebral column. Although cordotomy is sometimes effective for this type of pain, the long-term results do not approach those obtained with DREZ lesions.

Another type of central pain that has responded to DREZ lesions is postamputation pain (75,78,79,83,84,87,88). Within this category are two different types of pain syndromes: stump pain and phantom limb pain (88,89). The overall results for postamputation pain are 39% success in a group of 28 patients. In the series of Saris et al., phantom limb pain was highly likely to respond (six of nine patients), whereas stump pain was never relieved (zero of six patients) (88). When phantom limb pain and stump pain were both present, good results were noted in two of seven patients, but only the phantom pain responded regularly. None of the other reports clearly discriminated between phantom limb pain and stump pain. Because of the aforementioned failures, DREZ lesion is not highly recommended for stump pain.

In the earlier reports on the use of DREZ lesion for postherpetic neuralgia, Nashold and associates (86,87,90) reported that 10 of 17 patients (59%) had good pain relief

accompanied by a complication rate of 35%. In patients who had postherpetic pain for 6 months to 11 years and were followed 6 months to 6 years postoperatively, 29 (91%) had immediate relief. At 6 months, however, the figure dropped to 17 (53%), and at 18 months and thereafter only eight (25%) had persistent relief of postherpetic neuralgia involving the spinal nerves (81). Thirty-one patients with various myelopathies and neuropathies have also been treated with DREZ lesions (71,72,91,92). Approximately two-thirds had good results, with follow-ups of 6–19 months and a complication rate of 10–20%.

Nashold and associates (93,94) reported the use of DREZ lesions on the subnucleus caudalis for the treatment of severe postherpetic neuralgia and other severe intractable facial pain. After laminectomy of the C-1 to C-3 vertebrae and a small suboccipital craniectomy, the lesion is made to extend from the upper dorsal rootlet of C-2 to the tuberculum cinereum, slightly rostral to the level of the obex and the fourth ventricle. Production of DREZ lesions in the subnucleus caudalis also entails destruction of the descending trigeminal tract; the anatomical correlate of pain relief is unclear (88,93).

Since 1989, there have been at least 46 reported operations for facial pain using a two-electrode technique for subnucleus caudalis DREZ lesions. The overall pain relief was noted as “excellent” in 34% of patients and good in another 40%. The best results were obtained in patients with postherpetic pain involving one or more divisions of the trigeminal nerve (95). Pain resulting from facial trauma or dental surgery was not improved. In general, deafferentation pain responds to lesioning, but pain of a peripheral origin does not.

As more reports continue to be published regarding DREZ lesions, clear indications become more apparent for DREZ lesions in the management of chronic pain. The DREZ lesion is the only operation that was specifically designed to treat central and deafferentation pain. It is widely recognized that all standard ablative neurosurgical procedures are much more effective against pain associated with nociception (especially cancer pain) than they are against peripheral-central pain states. It remains unclear whether DREZ lesions are useful in patients with cancer pain; dorsal rhizotomy seems to be a less formidable operation for denervation of the painful area. The results of rhizotomy are variable, however, and it remains unclear whether the addition of ganglionectomy can improve them. Perhaps DREZ lesions will be effective in this type of pain.

More than any other ablative procedure, use of DREZ lesions can achieve variable results because of differences in lesion placement. It is not known how many segments above or below the level of injury the lesions should be made. Patients who have failed to obtain good pain relief might continue to suffer because the lesions did not extend far enough rostrally or caudally, yet the failure to relieve pain is ascribed to a deficiency of the operation itself. The poor results that sometimes follow DREZ lesions could be caused by failure of the surgeon to destroy the necessary amount of tissue or could be a result of inherent shortcomings in the operation as a concept (74).

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8

ASSESSMENT AND MANAGEMENT OF CANCER-RELATED FATIGUE

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Fatigue is among the most common symptom experienced by patients with cancer. In fact, the prevalence of fatigue ranges from 70–100% in patients receiving cancer treatment (1,2,3,4 and 5). Fatigue is often identified by patients as a major impediment to function and quality of life.

Although recognized by clinicians as a significant clinical problem, there is a striking lack of empirical research on fatigue. The epidemiology is poorly defined, and the range of clinical presentations remains anecdotal. The possibility of discrete fatigue syndromes linked to specific predisposing factors or potential etiologies, and described by unique phenomenologies and pathophysiologies, has not been explored. Indeed, there are very few data available to confirm the importance of any particular etiology, and pathophysiological mechanisms for cancer-related fatigue are entirely conjectural. Perhaps most important, there have been almost no clinical trials of putative therapies for fatigue. Treatment, when it is offered, is based largely on extrapolation of data from other clinical settings and anecdotal experience.

The obvious complexity of fatigue in the medically ill, combined with the lack of research, complicates efforts to define and characterize the symptom and offer clinical guidelines for assessment and management. Nonetheless, it is important to begin this process and thereby increase the visibility of fatigue as a clinical problem and the willingness of clinicians to explore therapeutic options. In this regard, an abundant theoretical literature can be heuristic (6,7,8,9,10,11,12,13,14,15 and 16).

DEFINITION OF FATIGUE

Fatigue is a symptom and, as such, is inherently subjective. No clear consensus exists about the nature or duration of the phenomena that would warrant the diagnosis of a fatigue syndrome or the utility of functional impact as a defining characteristic. Although clinicians generally appreciate that the differentiation between the “normal” fatigue experienced commonly by the population at large and clinical fatigue associated with a disease or its therapy requires specific criteria related to phenomenology, severity, duration, or impact, none of these potential criteria has been evaluated sufficiently to determine a definition on empirical grounds. Indeed, one definition suggests that fatigue is a feeling of weariness, tiredness, or lack of energy that varies in degree, frequency, and duration (2).

Recently, a multidisciplinary panel of clinicians and researchers convened by the National Comprehensive Cancer Network developed practice guidelines for cancer-related fatigue. The Fatigue Practice Guidelines Panel defined cancer-related fatigue as “an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning” (17). In addition, cancer-related fatigue was accepted as a diagnosis in the *International Classification of Diseases, 10th Revision, Clinical Modification*. Fatigue may be classified as a multidimensional phenomenon that develops over time, diminishing energy, mental capacity, and the psychological condition of cancer patients (Table 8-1) (18).


The following symptoms have been present every day or nearly every day during the same 2-wk period in the past month:
- Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level

Plus five (or more) of the following:
- Complaints of generalized weakness or limb heaviness
- Diminished concentration or attention
- Decreased motivation or interest in engaging in usual activities
- Insomnia or hypersomnia
- Experience of sleep as unrefreshing or nonrestorative
- Perceived need to struggle to overcome inactivity
- Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued
- Difficulty completing daily tasks attributed to feeling fatigued
- Perceived problems with short-term memory
- Postexertional malaise lasting several hours

The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

There is evidence from the history, physical examination, or laboratory findings that the symptoms are the consequence of cancer or cancer-related therapy.

The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium.

Adapted from Cella D, Peterman A, Passik S, et al. Progress toward guidelines for the management of fatigue. Oncology 1998;12(3A):369–377; with permission.

TABLE 8-1. CRITERIA FOR CANCER-RELATED FATIGUE

EPIDEMIOLOGY OF CANCER-RELATED FATIGUE

Although there are obvious problems in performing valid surveys of a symptom that is yet poorly defined clinically, an abundance of observations in the cancer population together affirm that fatigue is both extremely prevalent and protean in its presentation. The current data are very limited, however, and there continues to be little known about the factors that may predispose to fatigue or produce it, the comorbidities that may influence its expression, and the impact it has on the quality of life of cancer patients.

Among those with metastatic disease, the overall prevalence rate for the complaints of diminished energy or fatigue has been reported to exceed 75% (19,20,21,22,23 and 24). A cross-sectional survey of 151 patients with ovarian cancer that evaluated symptom prevalence and characteristics (19) observed that fatigue during the past week was reported by 69% and that approximately one-half of those who experienced it described it as highly distressing.

A recent population-based survey of 419 randomly selected cancer patients, 31% of whom had been diagnosed during the past year, revealed that 78% experienced fatigue (defined as debilitating tiredness or loss of energy at least once each week) (25). Two-thirds of these patients reported that the symptom “significantly” (31%) or “somewhat” (39%) affected daily routine.

Some surveys have linked the occurrence of fatigue to specific antineoplastic therapies (5,7,15,16,26,27,28,29 and 30). The prevalence rates from these surveys must be viewed as tentative because of methodological concerns, including the use of nonvalidated assessment techniques in some and, in most cases, the inability to control for a variety of intercurrent phenomena such as other treatments, changes in the disease, and new-onset medical or psychosocial problems. Nonetheless, these surveys suggest that fatigue can occur after surgery, chemotherapy, radiotherapy, and immuno-therapy. Prevalence rates as high as 96% have been reported in association with chemotherapy and radiotherapy (7), and severe fatigue has been described as a near constant phenomenon associated with some of the biological response modifiers, such as interferon-a and interleukin-2 (15,16,30). A relationship between the timing of treatment and the course of fatigue has been observed in several studies (5,29), providing perhaps the strongest evidence of a causative role for the treatment.

Fatigue has been anecdotally associated with many other potential etiological factors (Table 8-2), but little is known about the incidence and prevalence of the symptom when these factors exist. Although there is good evidence, for example, that fatigue can be caused by anemia (31), little is known about the relationship between the extent or rate of hemoglobin loss and the development of fatigue. Fatigue also has been associated with many types of major organ dysfunctions, including severe

cardiac or pulmonary diseases, renal failure, or hepatic failure. Hypothyroidism and adrenal insufficiency, even if relatively mild, may also be etiologically important. Neuromuscular disorders, such as polyneuropathy or Eaton-Lambert syndrome, are also associated with fatigue. More commonly, fatigue is associated with a sleep disorder, systemic infection, the use of centrally acting drugs such as opioids, poor nutrition, or cachexia. It is possible that these factors, too, are involved in the pathogenesis of fatigue. Finally, there is a well-recognized association between fatigue and major depression.

Medical/physical conditions
Associated with the underlying disease itself
Associated with treatment for the disease
Chemotherapy
Radiotherapy
Surgery
Biological response modifiers
Associated with intercurrent systemic disorders
Anemia
Infection
Pulmonary disorders
Hepatic failure
Heart failure
Renal insufficiency
Malnutrition
Neuromuscular disorders
Dehydration or electrolyte disturbances
Associated with sleep disorders
Associated with immobility and lack of exercise
Associated with chronic pain
Associated with the use of centrally acting drugs (e.g., opioids)
Psychosocial factors
Associated with anxiety disorders
Associated with depressive disorders
Stress-related
Related to environmental reinforcers

TABLE 8-2. POSSIBLE PREDISPOSING FACTORS OR ETIOLOGIES OF CANCER-RELATED FATIGUE

Systematic surveys that could confirm the importance of these anecdotal associations have not been performed. Consequently, neither the nature of these relationships nor their importance relative to each other is known. Their utility in developing a therapeutic strategy (see “Management of Fatigue”) underscores the need for more research.

The relationships between fatigue and other patient characteristics, including demographics and psychosocial factors, also have been explored very little and there are no reliable conclusions. Older age, more advanced disease, and combined modality therapy have been associated with fatigue in one survey (27), and psychological distress was associated in another (5). There continues to be a need for systematic prospective surveys that can confirm and expand these observations.

There are many parallels between cancer and other incurable, progressive diseases, such as acquired immunodeficiency syndrome (AIDS). There is little information about the epidemiology of fatigue in these other disorders. A recent study of 427 ambulatory patients with AIDS (32) suggests the importance of such research. The prevalence of fatigue was 54%, and there were strong associations found between the occurrence of fatigue and the number of AIDS-related physical symptoms, current treatment for human immunodeficiency virus–related medical disorders, anemia, and pain. In this study, AIDS patients with fatigue were also observed to have relatively poorer physical functioning and quality of life and relatively greater psychological distress than those who reported no fatigue.

PATHOGENESIS OF FATIGUE

The mechanisms that precipitate or sustain fatigue in the cancer population are not known. The diversity of factors that may predispose to fatigue, cause it directly, or influence its expression, combined with the equally complex phenomenology of the symptom, suggest that it is not one disorder with a single mechanism. Rather, it is more likely that the fatigue associated with cancer or other medical illnesses actually represents a final common pathway to which many mechanisms may potentially contribute (6,8,9,11,12,13 and 14).

On theoretical grounds, it may be proposed that some fatigue is caused by abnormalities in energy metabolism related to increased need, decreased substrate, or the abnormal production of substances that impair intermediate metabolism or the normal functioning of muscles. Increased need, for example, could be associated with the hypermetabolic state that can accompany tumor growth, infection, fever, or surgery. Decreased substrate may account for the fatigue associated with anemia, hypoxemia of any cause, or poor nutrition.

Based on limited studies of muscle function in cancer patients, it has been suggested that some fatigue could be related to abnormal accumulation of muscle metabolites, such as lactate (33). There is no evidence linking this mechanism to fatigue, however, and if it were to occur, it could still reflect an epiphenomenon related to more fundamental disruption in metabolic activity. The mechanisms that have been most intensively studied involve the production of cytokines, such as tumor necrosis factor and others. There is good evidence that these compounds play a role in the cachexia experienced by some patients with cancer or AIDS (34). The link between cachexia and fatigue observed in the clinical setting, combined with the fatigue that often accompanies the exogenous administration of the biological response modifiers when used as cancer therapy, suggests that similar mechanisms may be involved in the pathogenesis of at least some types of fatigue (35). At the present time, however, there is no direct evidence that any cytokine is causally related to the occurrence of fatigue. Measurement of these and other biochemical factors concurrent with systematic symptom assessment is needed to confirm the relationship.

Other mechanisms for fatigue probably exist as well. Changes in the efficiency of neuromuscular functioning could occur as a direct result of neurological diseases, such as peripheral neuropathy, and result in fatigue. It is interesting to speculate that the fatigue sometimes reported in association with immobility and lack of exercise may also be due to reduced efficiency of neuromuscular functioning.

A sleep disorder could possibly cause disturbed arousal mechanisms, or equally plausible, be an indicator of a disorder of arousal. These disorders could be primary or related to metabolic disturbances or the use of centrally acting drugs. In a recent study (36), the relationships between daytime inactivity and nighttime restlessness and cancer-related fatigue were evaluated in 72 women who were undergoing the first of three cycles of chemotherapy after surgery for stage I/II breast cancer. Women who were less active during the day and who had more nighttime awakenings consistently reported higher levels of cancer-related fatigue at the midpoints of each chemotherapy cycle. In addition, the number of awakenings had the strongest association with the severity of fatigue. Additional work is warranted to determine the exact role that sleep disturbance and/or activity intolerance plays in the development of cancer-related fatigue.

Finally, it may be useful to postulate a mechanism of fatigue that may be specifically related to an affective disorder. The improvement in fatigue often noted by patients who were successfully treated for a major depression provides some support for this speculation.

Ultimately, it may be possible to assess the fatigue reported by a patient with cancer and infer from this assessment the nature of the underlying mechanism(s). This approach may in turn provide new avenues for therapies targeted to the specific mechanisms involved. A great deal more research is needed before this goal can be attained.

ASSESSMENT OF FATIGUE

Fatigue is a subjective, multidimensional symptom associated with a broad spectrum of physiological disorders. Detailed characterization of the symptom, combined with an understanding of the most likely etiological factors, is needed to fashion a therapeutic strategy that aims to minimize or reverse the likely causes and provide whatever symptomatic therapies are practicable. From this perspective, fatigue is similar to other prevalent symptoms in the cancer population (37). The clinical literature on symptom assessment is most developed for cancer pain, and the guidelines that have been developed for pain assessment offer important lessons for the assessment of fatigue.

Assessment of Fatigue Characteristics

The comprehensive assessment of fatigue begins with a detailed description of its phenomenology and the elaboration of hypotheses concerning etiology and pathogenesis. This information is acquired through the history, physical examination, and review of laboratory and imaging studies.

As noted, fatigue is multidimensional. Some of the dimensions that could be used to characterize fatigue are like those that could be applied to any other symptom, such as severity or associated distress. Other dimensions, however, are unique to this symptom and reflect the complexity incorporated into the definition of this phenomenon (Table 8-1).

As discussed previously, patients may describe fatigue in terms that relate to lack of vitality, muscular weakness, dysphoric mood, somnolence, or impaired cognitive functioning. Commonly, the description will focus on several disturbances. The history should clarify the spectrum of complaints and attempt to characterize features associated with each component. In some cases, this information will suggest an approach to therapy. For example, a patient may report a sense of diminished energy

throughout the day and somnolence in the morning. If the latter symptom can be related to a nighttime medication, such as an antidepressant, a treatment strategy could be developed that would first address the morning symptoms by changing the drug regimen and then attempt to manage whatever residual fatigue remained.

The distinction between acute fatigue and chronic fatigue is clinically relevant. Acute fatigue has a recent onset and is anticipated to end in the near future. Chronic fatigue may be defined as fatigue that persists for a period of weeks and is not anticipated to remit soon. Although there is obvious imprecision in this distinction, it is important in therapeutic decision making. A patient who is perceived to have chronic fatigue typically warrants a more intensive assessment and an approach to management focused on long-term as well as short-term goals.

Other temporal features, such as onset and course, are also clinically relevant. Fluctuation in the levels of fatigue that is linked to a discrete event, such as the administration of an antineoplastic therapy, is strong evidence of causation.

Information about factors that exacerbate or relieve fatigue should be specifically queried. Like the course over time, this information may suggest an etiology or pathophysiological mechanism or may be therapeutically relevant.

In clinical practice, the assessment of fatigue must always include an evaluation of severity. This assessment can be accomplished using a verbal rating scale (none, mild, moderate, severe) or an 11-point numeric rating scale (where 0 equals “no fatigue” and 10 equals “the worst fatigue imaginable”). The clinician should adopt one scale and use it consistently over time. The patient should be given a specific frame of reference when responding. For example, the patient might be asked to indicate the level of fatigue on average during the past week. The clinician can choose a different frame of reference, if this is desired, as long as the same instructions are given whenever the patient is evaluated.

Instruments for the Assessment of Fatigue

Unidimensional fatigue measurement typically focuses on severity (Fig. 8-1). In addition to the common four- or five-point verbal rating scales and numeric scales, visual analog scales (also called a *linear analog scale assessment*) may be used. The linear analog scale is typically a 100-mm line anchored on the ends with disparate word descriptors (e.g., “no fatigue” and “worst fatigue imaginable”). The psychometrics of a linear analog and a numeric scale have been evaluated in a medically ill population (38). Verbal rating scales and numeric scales have been incorporated into many symptom checklists (39,40 and 41).

FIGURE 8-1. Examples of unidimensional measures of fatigue severity. ECOG, Eastern Cooperative Oncology Group.

Other types of unidimensional scales have been used to assess fatigue severity. The validated quality-of-life measure created for the European Organisation for Research and Treatment of Cancer, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, has a subscale for fatigue that may be used independently (42). The three items in this subscale (Were you tired? Have you felt weak? Did you need a rest?) are graded on four-point verbal rating scales, and the sum provides the global score. The nine-item Fatigue Severity Scale (43) and the vigor/fatigue subscale of the Profile of Mood States (44) also measure global fatigue severity. An older scale, the Pearson-Byars Fatigue Checklist, has been used in studies of cancer patients but was validated in a healthy population and has been supplanted by newer measures (45).

Multidimensional fatigue questionnaires provide information about a range of characteristics other than intensity (46). There are now many validated instruments of this type (Table 8-3) (43,47,48,49,50,51,52,53,54 and 55).

Piper Fatigue Scale (47)
Lee Fatigue Scale (48)
Fatigue Assessment Questionnaire (49)
Functional Assessment of Cancer Therapy—Anemia/Fatigue (50)
Fatigue Symptom Inventory (51)
Brief Fatigue Inventory (52)
Cancer Fatigue Scale (53)
Schwartz Cancer Fatigue Scale (54)
Multidimensional Fatigue Inventory (55)

TABLE 8-3. MULTIDIMENSIONAL FATIGUE QUESTIONNAIRES

There are advantages and disadvantages in selecting a multidimensional assessment instrument. Most important, multidimensional assessment allows analyses that potentially clarify the nature of a fatigue syndrome or the type of response that occurs after an intervention. For example, a multidimensional instrument could help clarify the extent to which an intervention such as epoetin alfa affects fatigue in general, the cognitive component of fatigue, or mood.

There also may be disadvantages. Although all of the validated multidimensional assessment questionnaires have been developed in the cancer population, there has been no validation in other populations and no studies to determine the extent to which the different instruments measure similar constructs in the same population. Without these data, there is a possibility that the information collected during a study may not reflect validly on the population or scientific question. Each questionnaire covers a differing set of domains, and investigators must review a measure carefully before assuming that it addresses the issues relevant to the specific study. For example, many questionnaires do not assess sleep disturbance, mood disturbance, or cognitive impairment, and some do not evaluate fatigue-associated distress, temporal characteristics (e.g., onset, duration, fluctuation, course), or factors that worsen or relieve the fatigue.

To complement a multidimensional questionnaire, specific items can be developed, or additional validated questionnaires can be added to the questionnaire packet. The use of single items is simpler, but must be recognized as face valid only.

Other Fatigue-Related Evaluation

Identification of factors that may be contributing to the fatigue can suggest the use of a specific primary therapy directed to the etiology itself. All patients should undergo a medical and neurological examination and an evaluation of psychological status. Most patients should be screened for hematological or metabolic disturbances that may be relevant. The degree to which this and other types of laboratory or radiographic evaluation is pursued must be decided on a case-by-case basis. An extensive and costly evaluation that may be burdensome to the patient is justified only when the etiology is uncertain and the findings of the evaluation could lead to a change in therapy.

Assessment of Related Constructs

The occurrence of fatigue in the context of a progressive medical illness obligates the clinician to assess the symptom in a broader context. Chronic cancer-related fatigue cannot be addressed clinically without an understanding of the patient's overall quality of life, symptom distress, and the goals of care. These constructs constantly inform decision making.

Quality of life is itself a subjective, multidimensional construct that reflects the overall perception of well-being. It is related to the experience of suffering. The most relevant dimensions that contribute to quality of life or the degree of suffering pertain to physical, psychological, social, and existential or spiritual concerns (54,55). To fully characterize the impact of fatigue, the assessment should attempt to discern the degree to which this symptom contributes to impairment in quality of life and, concurrently, identify other factors that may be equally or more important. These factors may include other symptoms, progressive physical decline, independent psychological disorders, social isolation, financial concerns, spiritual distress, or others. This larger assessment allows the development of a therapeutic strategy that should be more likely to yield improved quality of life, or reduced suffering, than one focused entirely on a single symptom.

In assessing physical and psychological concerns, it is important to recognize that most cancer patients experience multiple symptoms concurrently (19,20). Studies have generally demonstrated that pain, fatigue, and psychological distress are the most prevalent symptoms across varied cancer populations. The construct of global symptom distress has been useful to characterize overall symptom burden (39,40 and 41), and in some situations, it is useful to consider symptom distress as the critical issue when addressing an impairment in quality of life. Patients who report fatigue should always be queried about the presence of other symptoms.

The issues encountered in the assessment of fatigue may also be clarified by another construct, the goals of care. At any point during the course of the disease, the patient, the patient's family, and clinicians may emphasize one or more of the major goals in this setting: (a) to cure or prolong life, (b) to maintain function, or (c) to provide comfort. The assessment of the goals of care derives from both the patient's desires and knowledge of the medical realities. Lack of clarity or disagreement about the goals of care can skew the assessment process and undermine the relationship with the patient and family. To avoid these problems, ongoing assessment of the goals of care and communication with the patient and family about these goals must be considered among the most important and challenging aspects of patient care.

MANAGEMENT OF FATIGUE

The comprehensive assessment of the patient with cancer-related fatigue allows the development of a strategy that attempts to ameliorate this symptom while addressing the therapeutic requirements posed by the disease itself and the need to provide other elements in the broader approach to palliative care. In some cases, therapy for fatigue should be aggressively pursued, whereas in others, interventions for fatigue can be subordinated to other therapeutic imperatives. These priorities should be developed collaboratively with the patient.

An algorithm for the treatment of fatigue has been developed based on the limited existing data and clinical experience (Fig. 8-2A and Fig. 8-2B) (56). After setting realistic expectations, the fundamentals include decisions about treatment for potential contributing causes and decisions about a variety of symptomatic therapies, both pharmacological and nonpharmacological.

FIGURE 8-2. A, B: Algorithm proposed for the treatment of cancer-related fatigue. Hgb, hemoglobin. (Adapted from Portenoy RK, Itri LM. Cancer-related fatigue: guidelines for evaluation and management. *Oncologist* 1999;4:1–10, with permission.)

Establishing Realistic Expectations

Education of the patient about the nature of fatigue, the options for therapy, and the anticipated results is an essential component of any therapeutic approach to fatigue (see Patient Education). In some situations, such as fatigue associated with advanced disease and organ failure, there are limited expectations for reversal of the symptom and this should be explained to the patient as part of a plan to improve adaptation. If there is reason to believe that the fatigue will be transitory, this information alone can sometimes suffice as therapy.

Primary Interventions

Interventions for fatigue can involve primary management of factors that are believed to be causally related, symptomatic interventions, or both. Although the range of factors associated with fatigue (Table 8-2) offers many opportunities for primary interventions, the decision to pursue a specific therapy is often difficult. None of these interventions has been studied as primary treatments for fatigue. The assessment of fatigue frequently reveals many potential factors, and their relative importance is often unclear. In the medically frail, interventions must be undertaken cautiously. The trial-and-error process of manipulating first one and then another contributing factor can be time-consuming and frustrating for the patient. Some of the potential causes for fatigue, such as the use of centrally acting drugs, are extremely prevalent, and it is often difficult to justify efforts to alter these factors when there is risk in doing so and they are so commonly used without the complication of fatigue.

Some primary interventions pose relatively little burden for the patient. The threshold for implementing these interventions is low. For example, all patients who complain of fatigue should undergo review of the drug regimen. Centrally acting drugs that are not essential should be eliminated or reduced. Polypharmacy is extremely common, particularly in the setting of advanced cancer, and there is often a tendency to continue drugs that have questionable benefit due to concerns about worsening symptoms if they are stopped. The experience of fatigue shifts the therapeutic index and clearly justifies a trial of dose reduction, at the least. The drugs that are usually considered in this case include antiemetics, hypnotics or anxiolytics, antihistamines (H_1 or H_2 blockers), and analgesics. If pain is controlled with an opioid, the experience of distressing fatigue often justifies cautious dose reduction (e.g., 25% of the total daily dose) to determine whether fatigue improves without worsening pain.

The threshold for intervening in an effort to reduce physical inactivity, insomnia, some metabolic abnormalities, or depressed mood is also usually low. The suggestion of exercise, if possible, and nonpharmacological therapy for a sleep disorder are often accepted enthusiastically by patients (see the section Symptomatic Therapy: Nonpharmacological Approaches). The use of a hypnotic can be useful but clearly requires careful monitoring. If sleep duration increases but the patient perceives it to be nonrestorative, the desired goal has not been achieved. As might be expected, the use of a centrally acting hypnotic may worsen daytime fatigue.

Fatigue can be associated with varied metabolic disturbances. Some, such as the metabolic derangements associated with renal failure, may not be treatable in the context of the overall disease. Others, such as dehydration, hypercalcemia, hypothyroidism, hypocortisolism, or hypoxia, can be managed at little risk. Interventions to improve these disturbances may be warranted in the overall approach to the fatigued patient.

A trial of an antidepressant in a fatigued patient with major depression is strongly indicated. More challenging is the decision to implement antidepressant therapy in the patient who has dysphoric mood but is not anhedonic and lacks other psychological criteria for the diagnosis of major depression. Although there are some risks with this therapy, most clinicians perceive that a treatment trial is warranted with any significant degree of depressed mood, particularly if there are other targets for the drug, such as anxiety or pain. In the setting of fatigue, the use of a relatively less sedating antidepressant, such as one of the serotonin-selective reuptake inhibitors, is appropriate. Bupropion or one of the secondary amine tricyclic antidepressants, such as desipramine, are alternatives to this class.

Recent evidence suggests that anemia may be a major factor in cancer-related fatigue. Anecdotally, transfusion therapy for severe anemia is often associated with substantial improvement in fatigue. Treatment with recombinant human erythropoietin offers another approach to this problem. In three randomized, placebo-controlled trials that enrolled a total of 413 patients, patients who were treated with erythropoietin for 8–12 weeks and experienced an increase in hematocrit of ³6% demonstrated significantly improved energy level, daily activities, and overall quality of life (57). The quality-of-life scores improved approximately 24% from baseline values. An open-label study of 2349 patients undergoing cytotoxic chemotherapy at >500 community oncology practices (31) demonstrated that erythropoietin treatment for up to 16 weeks was associated with significant increases in energy level, activities, and overall quality of life. These changes were correlated with the improvement in hemoglobin and not tumor response.

In a more recent study of 2370 patients with nonmyeloid cancers who were receiving chemotherapy (58), the effectiveness of administering erythropoietin as an adjunct to chemotherapy was evaluated in a prospective fashion. Patients received erythropoietin, 10,000 units three times weekly, which could be increased to 20,000 units three times weekly depending on the hemoglobin response at 4 weeks. Patients who experienced an improvement of >10 points in their overall quality of life demonstrated a 20–25% reduction in their levels of fatigue as measured by the FACT-An questionnaire.

These data are encouraging and suggest that patients with significant fatigue and hemoglobin levels that are not usually considered problematic (a level £12) should be considered for a trial of erythropoietin. Further studies are needed to illuminate the association between varying degrees of anemia and fatigue and clarify the extent to which hemoglobin must rise to obtain symptomatic benefit. Although erythropoietin is a relatively safe therapy, it is extremely expensive and is difficult to justify if either the fatigue or the anemia is mild, life expectancy is short, or there are other treatable factors that appear to be major contributors to the fatigue.

Symptomatic Therapy: Pharmacological Approaches

Although pharmacological therapy for fatigue associated with medical illness has not been evaluated in controlled studies, there is evidence supporting the use of several drug classes for this indication. The utility of the psychostimulants has been suggested in studies of methylphenidate and pemoline (59,60). There is a substantial clinical experience with these drugs in the treatment of opioid-related cognitive impairment (59) and depression in the elderly and medically ill (61,62,63 and 64). Although the evidence that psycho-stimulants can improve cancer-related fatigue is not conclusive, there is a favorable enough anecdotal experience to warrant a trial in patients who lack contraindications.

In the cancer population, the largest experience is with methylphenidate. Dextroamphetamine, pemoline, and modafinil have also been used anecdotally. There have been no controlled comparisons of these drugs and clinical experience suggests that the response to one does not necessary predict responses to the others. For this reason, sequential trials may be valuable to identify the most useful drug.

Pemoline is a novel psychostimulant with relatively less sympathomimetic activity than the other psychostimulants. This drug is available in a chewable formulation that can be absorbed through the buccal mucosa and may be useful in patients who are unable to swallow or absorb oral drugs. There is, however, a very small risk of severe hepatotoxicity from pemoline that has not been reported with the other psychostimulants (65). This risk may justify the use of methylphenidate as the first-line psychostimulant for most patients.

The potential toxicities associated with the psychostimulants include anorexia; insomnia; anxiety, confusion, and other organic brain syndromes; tremor; and tachycardia. These effects can be particularly problematic in the medically ill, who may be predisposed to the same symptoms for other reasons. Relative contraindications include preexisting anorexia, severe insomnia, anxiety or agitation (particularly if associated with paranoid ideation), and significant heart disease. To ensure safety, dose escalation of the psychostimulants should be undertaken cautiously, and at intervals long enough to evaluate the full gamut of potential toxicities.

In medically fragile patients, the initial dose of methylphenidate is usually 2.5–5.0 mg once or twice daily. This dose is gradually escalated until favorable effects occur or toxicity supervenes. Most patients require low doses; doses above 60 mg per day are very uncommon. Effects sometimes wane over time, a change that could reflect tolerance or progression of the underlying cause of the fatigue, and dose escalation may be needed to maintain effects. The risk of toxicity increases with the dose, however, and the ability to regain lost efficacy may be limited. The starting doses for dextroamphetamine and pemoline are 2.5–5.0 mg and 18.75 mg, respectively, once or twice daily, and modafinil usually initiated at a dose of 100–200 mg in the morning.

The use of low-dose corticosteroids as a treatment for fatigue has also been supported empirically (66,67). This treatment is usually considered in the population with advanced disease and multiple symptoms. There have been no comparative trials of the different agents in this class. Therapy is usually undertaken with dexamethasone, 1–2 mg twice daily, or prednisone, 5–10 mg twice daily.

Amantadine has been used for the treatment of fatigue due to multiple sclerosis for many years (59). There is no experience with this drug in populations with other diseases. Nonetheless, amantadine has relatively low toxicity, and an empiric trial may be warranted in selected patients with refractory fatigue associated with other diseases.

As noted previously, a therapeutic trial with an antidepressant drug is clearly appropriate if fatigue is related to a clinical depression and an antidepressant that is relatively less likely to be sedating, such as one of the serotonin-specific reuptake inhibitors, secondary amine tricyclics, or bupropion, would be preferred. Some patients appear to experience increased energy disproportionate to any clear effect on mood during treatment with one of these drugs. Theoretically, these “activating” effects could be used to treat fatigue. There have been no clinical trials of these drugs with fatigue as an end point, however, and the potential benefit of these drugs in nondepressed patients remains to be studied. In the absence of any data, an empiric trial would be warranted only in cases of severe fatigue refractory to other measures.

Symptomatic Therapy: Nonpharmacological Approaches

As noted, all patients with distressing fatigue require education to set realistic expectations. This communication is the simplest of the diverse nonpharmacological approaches that can be used to manage this symptom. Although there have been empirical evaluations of these nonpharmacological therapies, anecdotal experience suggests that several types of interventions may be useful (Table 8-4). Studies are needed to evaluate the effectiveness of these techniques.

Patient education
Exercise
Modification of activity and rest patterns
Stress management and cognitive therapies
Adequate nutrition and hydration

TABLE 8-4. NONPHARMACOLOGICAL INTERVENTIONS TO MANAGE FATIGUE

Patient preferences must be considered in developing a nonpharmacological strategy for fatigue. Participation is unlikely unless the patient perceives a substantial chance of benefit and only modest burden. More than one type of nonpharmacological intervention may be useful depending on the etiology of the fatigue.

Patient Education

Patient education that contains both procedural and sensory information has been shown to be effective in reducing pain and improving outcomes (68,69,70,71 and 72). Inadequate information may lead to needless anxiety. As noted previously, the fatigued patient should receive information about the nature of the symptom, the options for therapy, and the expected outcomes. Many patients assume that the problem reflects worsening of the disease and information about alternative explanations, if any are identified, can be very reassuring. There are large individual differences in patients' preferences for information, and the effort to educate should be provided

that is appropriate to the patient's educational level and readiness to learn.

As part of the educational process, patients may find it beneficial to keep a diary of their fatigue. The diary may help clinicians and patients discern a pattern to the fatigue and monitor its severity. This information may be useful in developing a management plan that modifies specific activities and incorporates appropriate periods of rest.

Exercise

Of the nonpharmacological interventions for cancer-related fatigue, exercise has the strongest evidence of a therapeutic benefit (72,73). Five studies have been published (74,75,76,77,78 and 79) that evaluated the effects of exercise on fatigue in cancer patients who were receiving treatment. According to Mock (73), all of these studies demonstrated significantly lower levels of fatigue in patients who exercised compared with controls. However, data that would allow the selection of the most appropriate exercise program for patients with various types of cancer or cancer treatments are not available.

Some general principles should be followed when prescribing exercise for a cancer patient. The exercise prescription should be individualized and consider such factors as the patient's age, gender, physical condition, and any inter-current medical conditions that may affect the individual's ability to exercise. Anecdotally, the type of exercise that appears to be most beneficial in ameliorating fatigue is exercise that involves rhythmic and repetitive movement of large muscle groups. This effect is achieved through walking, cycling, or swimming. An exercise program should be initiated gradually and patients should not exercise to the point of exhaustion. Exercise needs to be done for several days out of the week for beneficial effects to occur.

Contraindications to low-intensity exercise include cardiac abnormalities, recurrent or unexplained pain, onset of nausea with exercise, extreme fatigability, or cyanosis. A referral to an exercise physiologist may be warranted to have a more thorough evaluation and a specific exercise prescription developed for each individual patient.

Modification of Activity and Rest Patterns

The use of a diary to assess fatigue may identify specific activities that are associated with increased levels of fatigue. This information can facilitate a plan to modify, schedule, or pace these activities throughout the day. Brief, scheduled rest periods may help to reduce fatigue. Naps should be allowed only during the day because a period of sleep in the late afternoon or evening may interfere with the patient's ability to sleep at night.

One of the most important interventions in the area of activity and rest pattern modification is an assessment for sleep disturbances and patient education about basic sleep hygiene principles. Again, education about sleep hygiene principles should be tailored to the individual patient. One of the fundamental principles is the establishment of a specific bedtime and wake time. A specific wake time appears to be particularly important in maintaining a normal sleep-wake rhythm. An additional strategy is the establishment of routine procedures before sleep. For example, patients may read a book or watch television before falling asleep (80).

Exercise on a consistent basis tends to improve sleep and promote deeper sleep. If exercise is also used, it should be performed at least 6 hours before bedtime. Intense exercise raises the body temperature for at least 6 hours and it appears preferable for this period to pass before sleep.

Additional sleep hygiene measures include reduced environmental stimuli (e.g., loud noises, light) and the use of diversional activities (e.g., music, massage) to promote sleep. Patients also should be instructed to avoid stimulants (e.g., caffeine, nicotine, steroids, methylphenidate) and central nervous system depressants (e.g., alcohol) before sleep (80).

Stress Management and Cognitive Therapies

Anxiety, difficulties in coping with cancer or its treatment, or sleep disturbances are some of the factors that may contribute to the development of fatigue. These factors may be ameliorated using stress-reduction techniques or cognitive therapies (e.g., relaxation therapy, hypnosis, guided imagery, distraction). Research has demonstrated that distraction (e.g., gardening, listening to music, taking quiet walks) may be effective in reducing the symptom, particularly for patients with fatigue associated with deficits in attention (81,82). A referral to a psychiatrist or a psychologist for counseling and training in stress management techniques or cognitive therapies may be warranted in some patients.

Adequate Nutrition and Hydration

Cancer and its treatment can interfere with dietary intake. Fatigued individuals also may underestimate the amount of food and fluid they ingest. To aggressively manage fatigue, patients' weight, hydration status, and electrolyte balance should be monitored and maintained to the extent possible. Regular exercise may improve appetite and increase nutritional intake. Referral to a dietitian for dietary planning and suggestions for nutritional supplements may be beneficial if one of the causes of fatigue is inadequate food or fluid intake.

CONCLUSION

Despite the high prevalence and distress associated with fatigue, there has been little recognition of this symptom as an important issue for research and clinical guideline development. At the present time, relatively little is known about its epidemiology, etiologies, and management. There is no definitive information about the types of mechanisms that may produce fatigue in discrete populations.

With burgeoning interest in palliative care, it is likely that increasing attention will focus on the problem of fatigue. Extensive research is needed before the symptom will be adequately characterized in terms of phenomenology, pathogenesis, and management.

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9

FEVER AND SWEATS

JAMES F. CLEARY

TEMPERATURE AND ASSOCIATED SYMPTOMS

Temperature has long been used in clinical medicine and was included in the cardinal signs of inflammation described as “tumor, rubor, dolor and fevor.” The measurement of temperature by thermometer, in the sublingual, subaxillary or rectal locations, is not a clinical skill practiced regularly by doctors. In most cases, temperature is recorded by other health workers or by patients themselves. Normal body temperature is considered to be 37°C, the average core temperature for an adult population.

Temperature is tightly controlled within a narrow range in each individual. Fever is defined as any elevation in core body temperature above the normal and results from the upregulation of body temperature. More commonly, a temperature greater that 38°C is considered a clinically significant fever. In oncological practice and many clinical studies, a significant fever is defined as single temperature reading greater than 38.5°C or three readings (at least an hour apart) of more than 38°C. The term *fever* (or pyrexia) *of unknown origin,*, FUO (PUO), is used commonly and often incorrectly in the daily practice of medicine. An FUO is defined as an illness lasting at least 3 weeks with a fever higher than 38°C on more than one occasion and which lacks a definitive diagnosis after 1 week of evaluation in a hospital (1).

Fever is often accompanied by other symptoms, including sweating and rigors. Sweating, when it accompanies fever, is a cooling response by the body in which heat is released from the body as it evaporates water on the skin's surface. Rigors and shivering also contribute to temperature control and are rapid muscle spasms designed to increase heat production within the body. For adult humans and most large mammals, shivering is the major means of increased heat production in response to a cold environment. Nonshivering thermogenesis, a process involving heat production in brown adipose tissue, is important in the temperature control of infants.

CONTROL OF TEMPERATURE

It is proposed that core body temperature is controlled by neurological mechanisms centered at the anterior hypothalamus. The onset of fever in patients results from an elevation of the body's regulated setpoint temperature through a resetting of the temperature “gauge” in the hypothalamus (2). This may be caused by various drugs or by endogenous pyrogens. As a result of the reset hypothalamic temperature, the body increases the core body temperature to this new level (Fig. 9-1) through shivering or nonshivering thermogenesis. The continued presence of pyrogen at the hypothalamus results in the maintenance of this higher temperature. Eventually, either as a result of a decrease in the quantity of pyrogen or the administration of an antipyretic, the hypothalamic temperature is reset back to a lower or normal level. The core body temperature is therefore lowered through sweating. This control mechanism may be suppressed in patients administered steroids or antiinflammatory agents. Older patients may not be able to mount the anticipated febrile response.

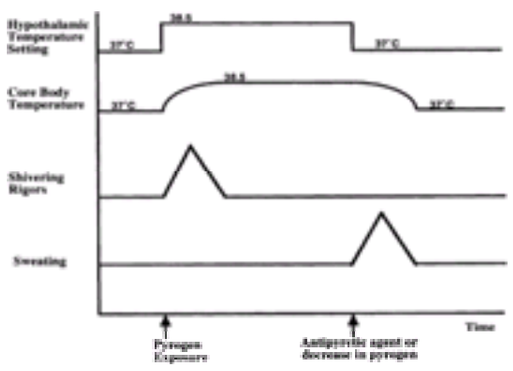

FIGURE 9-1. Physiological mechanisms associated with fever and accompanying symptoms. (Adapted from Boulant JA. Thermoregulation. In: Mackowiak P, ed. *Fever: basic mechanisms and management*. New York: Raven Press, 1991:1–22, with permission.)

The endogenous pyrogens that are responsible for the onset of fever are largely derived from monocytes and macrophages. These cells, as a result of challenge by either endotoxin or ineffective sources, release tumor necrosis factor (TNF) and interleukin-1 b(IL-1b). Their production is part of the complex cascade that results in the stimulation of other cytokines, such as interleukin-6 (IL-6), interleukin-8 (IL-8), and changes in prostaglandin metabolism. Serum levels of IL-6 and IL-8 have been found to correlate with core body temperature in febrile neutropenic patients (3). The ultimate end point of this cascade is the activation of granulocytes, monocytes, and endothelial cells. While fever appears to be associated with enhanced function of the immune system, it must nonetheless be noted that a direct connection between such phenomena and a beneficial effect of fever on outcome of infections has not been established. Fever, in fact, may be deleterious in the setting of autoimmune disorders or infections (4).

ETIOLOGY OF FEVER IN CANCER PATIENTS

Fever is commonly seen in cancer patients, both in those with and without infection. The wide range of etiologies of fever in cancer patients will be considered in relation to the pathophysiology of fever in these patients.

Tumor

Fever associated with tumor is believed to be associated with the release of pyrogens, either directly from a tumor or from stimulation of immunological mechanisms by the tumor, that cause an elevation in temperature through action on the anterior hypothalamus. The classical association of fever to particular tumor diagnoses relates more to tumors associated with a diagnosis of FUO (Table 9-1). In the combined results of six studies documenting the etiology of FUO, 23% of adults meeting the

defined diagnosis were found to have malignancy as the cause (c.f., 8% of children) (5). In another study of 111 elderly (age >65 years) patients with FUO, 26 had associated malignancy with 15 patients diagnosed with lymphoma and 4 with renal cell carcinoma (6). Almost 7000 cancer patients with fever were reviewed by Klastersky et al., and only 47 (0.7%) fit the diagnostic criteria for an FUO (7). Twenty-seven of the 47 had leukemia or lymphoma, with disease rather than infection being the cause of the fever in only 11. Tumor was responsible for fever in seven patients with widespread metastatic carcinomas; in six of these, large liver metastases were present.

Hodgkin's disease
Lymphoma
Leukemia
Renal cell carcinoma
Myxoma
Osteogenic sarcoma

TABLE 9-1. TUMORS CLASSICALLY ASSOCIATED WITH FEVER

Hodgkin's disease has classically been associated with the Pel Epstein fever (Fig. 9-2), where a patient experiences 3–10-day cycles of fever alternating with periods of normal temperature (8). Although the presence of fever is an important prognostic indicator in patients with Hodgkin's disease, there has been some discussion (9) about the value of Pel Epstein fever as a diagnostic tool particularly because the original description of the Pel Epstein fever was made in two patients who were subsequently found, on pathological review, not to have Hodgkin's disease.

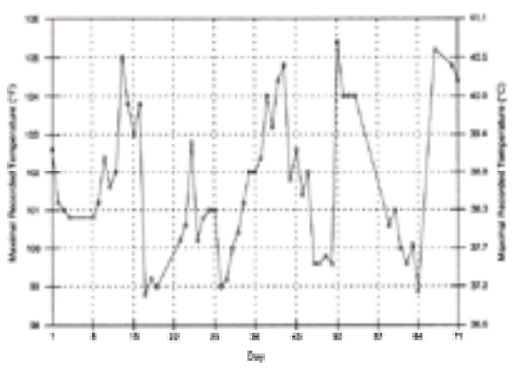

FIGURE 9-2. A 50-year-old man had fever, night sweats, and nonproductive cough for 10 weeks. He took antipyretic medications during the febrile periods. His wife recorded his temperatures, shown above, on 56 of the 71 days. Biopsy of a rapidly enlarging cervical lymph node revealed nodular sclerosing Hodgkin's lymphoma. The patient's fevers and other symptoms promptly disappeared after the first cycle of doxorubicin, bleomycin, vinblastine, and dacarbazine. [From Good GR, Dinubile MJ. Images in clinical medicine. Cyclic fever in Hodgkin's disease (Pel-Ebstein fever). *N Engl J Med* 1995;332:436, with permission.]

Although classical teaching is that fever is associated with particular tumors, fever also occurs in many of the more common cancers (Table 9-2). Forty-one percent of those who underwent autopsy had evidence of infection as an explanation of their fever (10). The incidence of infection among the autopsied patients was 50% for acute leukemia, 75% in lymphoma patients, and 80% in those with chronic lymphocytic leukemia. Infection was only found in a third of those with chronic myeloid leukemia, 17% with Hodgkin's disease, and 15% of patients with lung cancer.

Primary site	Number of patients observed	Number of patients with fever without associated infection	
		Number	%
Stomach	1498	573	41
Kidney	208	39	19
Colon and rectum	113	75	66
Liver and gallbladder	98	43	44
Uterus	81	19	36
Squamous skin cancer	41	20	49
Esophagus	20	7	35
Breast	48	16	33
Lung	17	8	47
Small bowel	17	1	6
Prostate	11	7	64
Bladder	10	6	60
Bone	10	7	70

From Boggs DR, Rai E. Clinical studies of fever and infection in cancer. Cancer 1968;1:1240–1261, with permission.

TABLE 9-2. INCIDENCE OF FEVER WITHOUT EVIDENCE OF INFECTION AT AUTOPSY IN PATIENTS OF DIFFERENT PRIMARY TUMOR TYPES

Infection (Including the Neutropenic)

While infection and fever can be a common presentation in cancer patients, it is of particular concern in neutropenic patients. Neutropenia, defined as a peripheral blood neutrophil count of less than 500/µl, results from either increased destruction or decreased production of white blood cells. Decreased production by the bone marrow may result from either disease involving the marrow or from myelosuppression by chemotherapy. The cause of fever is not identified in some 60–70% of neutropenic patients (11). Risk factors for the development of fever in the setting of neutropenia have been identified and include a rapid decrease in the neutrophil count and a protracted neutropenia of less than 500 cells/µl for greater than 10 days (12). Twenty percent of patients with 1 week of chemotherapy-induced neutropenia develop a fever and the rate of infection increases with lengthening periods of neutropenia. Other factors that may alter the risk of the neutropenic patient include phagocyte function, the status of the patient's immune system, and alterations in the physical defense barriers of the body (e.g., mucositis).

Fever and neutropenia in cancer patients are associated with a high risk of medical complications with a death rate ranging from 4–12%. Twenty-one percent of patients with febrile neutropenia at the Dana Farber Cancer Center developed serious medical complications (13). The investigators identified four risk groups for febrile neutropenic patients. Group 1 were inpatients at the time of onset of fever; group 2, outpatients who developed significant comorbidity within 24 hours of presentation; group 3, outpatients with uncontrolled cancer but without serious concurrent comorbidity; and group 4, outpatients without serious concurrent comorbidity and whose cancer was well controlled. The model was validated in 444 patients with febrile neutropenia, of whom 36% had a significant comorbidity, 27% had serious medical complications, and 8% died. Group 1 had the greatest risk and group 4 had little risk in relation to medical complications and risk (Table 9-3).

Patient group	Number of patients	Multiple complications (%)	Deaths (%)
Group I	258	51 (19)	25 (9)
Group II	43	3 (7)	5 (12)
Group III	29	3 (10)	4 (14)
Group IV	134	0 (0)	0 (0)
All patients	444	57 (13)	34 (8)

[a]Risk groups are defined in text.
From Talcott JA, Siegel RD, Finberg R, et al. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. J Clin Oncol 1992;10:316–322, with permission.

TABLE 9-3. INCIDENCE OF MULTIPLE MEDICAL COMPLICATIONS AND MORTALITY IN FEBRILE NEUTROPENIC PATIENTS AS DEFINED BY RISK [a]

An important component of this study was the identification within 24 hours of onset of fever of those patients at low risk of medical complication. These low-risk patients were indeed at risk of developing medical complications (5%). But they were either transient and asymptomatic or were heralded by at least 7 days of medical deterioration and were thus readily detectable by appropriate follow-up. Two additional risk factors—a latency period of less than 10 days from the time of chemotherapy administration to the onset of fever, and neutropenia and age greater than 40—correlated with the occurrence of more frequent complications. Mucositis was associated with decreased risk of medical complications, suggesting that infection associated with mucositis may be responsive to antibiotics. The identification of a causative organism or positive blood cultures was not associated with increased risk.

In a multinational study, a risk-index score was developed to “stage” those patients with febrile neutropenia (14). Predictive factors included blood pressure, presence of chronic obstructive pulmonary disease or solid tumor, previous fungal infection in patients with hematological malignancies, outpatient status, status of hydration, and age in relation to 60 years. On the validation set, a Multinational Association for Supportive Care in Cancer risk-index score ^{3} to 21 identified low-risk patients with a positive predictive value of 91%, specificity of 68%, and sensitivity of 71%. In a further population, the risk index accurately identified patients at low risk for complications. This risk index may be useful in the selection of patients for studies that test strategies to treat febrile neutropenia.

Based on a number of retrospective studies, similar definitions of low risk have been applied to pediatric patients with fever and neutropenia (15). Low risk included evidence of bone marrow recovery in culturenegative patients who were afebrile for at least 24 hours and who had no other reason to continue intravenous antibiotics in the hospital. The control of any localized infection and the patient's ability to return promptly in the event of fever or other complications were also necessary. In a prospective study of 70 patients who met the above criteria and who were discharged home with neutropenia, none was readmitted with fever. All seven patients who were inadvertently discharged without evidence of marrow recovery were readmitted with recurrence of fever. Neutropenic children with positive cultures were also assessed to identify risk factors for bacteremia (16). Of the cases of bacteremia, 92.5% occurred in those whose cancer was not controlled, were less than 1 year of age, were less than 10 days past their last chemotherapy, and who had no evidence of marrow recovery.

Organisms (Bacteriology)

A basic understanding of the classification and sensitivities of the different organisms is essential to the understanding of infection in cancer patients. Over time there have been changes in the underlying organisms associated with febrile neutropenia as evidenced by progressive studies by the EORTC group (17). Gram-negative organisms were the leading cause of infection in febrile neutropenic patients, but their incidence has decreased from 71% of identified causative organisms during the 1973–1978 period to 31% during the 1989–1991 period. Infection by one of these gram-negative organisms—*Pseudomonas aeruginosa*— has been a driving force in the selection of antibiotics. However, the incidence of pseudomonas infection has also decreased over the last few years as reflected by an incidence of only 0.1% of febrile neutropenic cases at the National Cancer Institute (18). The incidence of gram-positive organisms has increased from 29% during the 1973–1978 period to 69% during the 1989–1991 period, requiring a review in treatment regimens used in febrile neutropenic patients. The incidence of both acute and chronic fungal infections has also increased, with up to 33% of febrile neutropenic patients not responding to a week of antibiotic therapy, having a systemic fungal (*Candida* or *Aspergillosis*) infection (19).

Location

Infections can occur throughout the body and need to be sought carefully with history and examination. Collapse, consolidation, and superimposed infection may develop behind an obstructing bronchial tumor. Aspiration pneumonia may occur in those with esophageal tumor either secondary to an obstruction or as a result of a tracheoesophageal fistula.

The gastrointestinal system is the most common site of indigent organisms causing infection in neutropenic patients. *Clostridium difficile* infection may present with fever and diarrhea and must be considered in those who are already taking antibiotics. Fungal and viral infections of the esophagus need to be suspected in those with dysphagia and odynophagia. Anaerobic infections may be a factor in severe mucositis or gingivitis and in those patients with perianal discomfort. Spontaneous bacterial peritonitis may be a cause of fever in patients with ascites. A urinary catheter will increase the risk of urinary tract infection as does the presence of obstruction, but the presence of asymptomatic bacteriuria in a nonneutropenic cancer patient is not usually an indication for antibiotic treatment.

Central nervous system infections can be difficult to diagnose and usually require lumbar puncture to confirm. Infection is the most common complication of Ommaya reservoirs, used to administer intraventricular chemotherapy, and is more likely to occur in those with previous radiotherapy or in whom repeated surgical procedures have been necessary (20). Most infections are due to *Staphylococcus epidermidis* and usually can be successfully treated with antibiotics (21).

Particular attention to sites of recent surgery is important in assessing infection. Surgical collections may include infected hematomas that develop following surgery. The skin is also a common site of infection that may range from infected decubitus ulcers to herpes zoster infections. The use of catheters in oncology has created another portal for the introduction of infection in cancer patients. Of a total of 322 indwelling devices placed in 274 cancer patients by a single surgeon, device-related sepsis occurred in 28 of 209 patients (13%) with catheters and 6 of 113 patients (5%) with subcutaneous ports (22). Triple lumen catheters were associated with a higher rate of thrombosis but not of infection. The complications of 1630 venous access devices for long-term use in 1431 consecutive patients with cancer were reviewed (23). Of the catheters inserted, 341 of 788 (43%) had at least one device-related infection compared with 57 of 680 (8%) of the completely implanted ports (p = .001). The number of infections per 1000 device days was 2.77 for catheters compared with 0.21 for ports (p = .001). The predominant organisms isolated in catheter-related bacteremia were gram-negative bacilli (55%) compared with gram-positive cocci (65.5%) in port-related bacteremia. Patients with solid tumors were less likely to have device-related infectious morbidity compared with patients with hematological cancers.

Transfusion-Related

Blood products, administered extensively to cancer patients, may be associated with febrile reactions. The incidence of side effects following the administration of over 100,000 units of red blood cells to more than 25,000 cancer patients over a 4-year period was retrospectively reviewed (24). Of all transfused units, 0.3% had a transfusion-associated reaction; 51.3% were febrile nonhemolytic, and 36.7% were allergic urticarial reactions. Only 17 hemolytic reactions (4 immediate, 13 delayed) were documented. The incidence of transfusion-related side effects was significantly lower in this study than that reported in the noncancer population. Infection may also be a source of fever in patients receiving blood products. The Canadian Red Cross (25) estimated that the true positive rate of bacterial contamination of platelet concentrate units was between 4.4 and 10.7 per 10,000 units and recommended screening of all such units. The percentage of those patients developing bacteremia or septicemia from infected units was not discussed.

Thrombosis

Trousseau's self diagnosis of gastric cancer on the basis of venous thrombosis is a reminder that cancer patients are at particular risk of thrombosis. Deep-vein thrombosis may present with fever and, given the uncertainty of clinical diagnosis, investigation may be necessary in the “at risk” patient. Pelvic thrombophlebitis may sometimes occur after pelvic surgery and, if septic, may manifest with either low- or high-grade fever. Pulmonary embolus also needs to be considered in the differential diagnosis of fever in cancer patients. Of 97 patients with confirmed pulmonary embolus in the Urokinase PE Trial, 17 had associated malignancy (26). Of those with confirmed malignancy, 54% had a fever greater than 37.5°C and 19.6% had a fever greater than 38°C. Fortyone percent of the cancer patients had associated sweating. Pulmonary infarction, with the primary signs of tachypnea, tachycardia, and fever, may be a presentation of pulmonary thrombi. Other thrombotic syndromes, such as cerebral venous thrombosis, although associated with fever, are not common in the setting of malignancy.

Hemorrhage

Gastrointestinal bleeding may present with fever and should be considered in the differential diagnosis of a patient with low-grade fever and sweats. However, in a major review of fever in cancer patients (10), serious hemorrhage was followed by fever in a minority of cases; the usual sequence has been that of hemorrhage in an already febrile patient.

Drugs

Drug-associated fever is an illdefined syndrome in which fever is the predominant manifestation of an adverse drug reaction. It is normally a diagnosis of exclusion (27). The drugs commonly associated with fever are antibiotics, cardiovascular drugs, central nervous system drugs (e.g., phenytoin), cytotoxics, and immune therapy (either as biological response modifiers or growth factors). Antimicrobial agents were responsible for 46 of 148 drug-related fevers in a review of the experience of two hospitals in Texas and the United Kingdom with a mean lag time from initiation of treatment to onset of fever of 21 days (median, 8 days). For 11 cases of cytotoxic-induced fever, the mean lag time was 6.0 days with a median of 0.5 days. Shaking chills were more common with the administration of cytotoxic-associated fever than with other drugs (28).

Cytotoxics

There is a diverse range of cytotoxic drugs whose administration is associated with fever (Table 9-4). The febrile response to bleomycin was described in the original phase 1 studies (29) and characteristically occurs 3–5 hours after injection. It is more common after intravenous than after intramuscular injection. It is seen in approximately 25% of patients administered the drug. The fever becomes less frequent with repeated injections. An anaphylactic reaction manifested by hyperpyrexia, shock, hypotension, urticaria, and wheezing occurs in 1% of patients administered bleomycin (30). Fever following the administration of cisplatin was also reported in early clinical trials (31). Streptozocin administration may result in fever associated with chills, as can cytarabine and etoposide. Fever can occur after the administration of 5-fluorouracil and high-dose methotrexate. Confusion concerning the etiology of a fever arises more commonly in the situation of intensive chemotherapy regimens where neutropenic patients may be administered cytotoxic agents that cause fever. Awareness of the symptoms produced by the different agents assists in discerning the etiology of the fever.

Bleomycin	Mustine
Cisplatin	Mithramycin
Cytarabine	Streptozocin
Cyclophosphamide	Thiotepa
Etoposide	Vinblastine
5-Fluorouracil	Vincristine
Methotrexate	

TABLE 9-4. CYTOTOXIC AGENTS ASSOCIATED WITH FEVER AFTER ADMINISTRATION

Antibiotics

The antibiotics commonly associated with fever are the penicillins, cephalosporins, and amphotericin. In 50 patients administered at least 100 mg of amphotericin B over a minimum of 3 days, fever was experienced by 34% and chills by 56%, with rates of 2.6 and 3.5 mean episodes per patient per treatment course, respectively (32). In patients who had received 20 mg or more of amphotericin-B per day for at least 10 consecutive days, shivering was noted to occur first at the test dose, with the percentage of patients who shivered increasing with each successive dose and peaking at the fifth therapeutic dose (33).

Opioids

The intravenous injection of morphine is often associated with sweating, and vasodilatation, but not necessarily associated with fever. Fever may occur as a result of the interaction between pethidine and monoamine oxidase inhibitor, an interaction to be avoided. Drug withdrawal is associated with a syndrome that includes fever and needs to be suspected in febrile cancer patients in whom opioids have been suddenly stopped. Withdrawal from benzodiazepines may also be associated with fever.

Biological Therapy

Interferons (IFN) are associated with the development of fever (34). Partially purified IFN administered at low doses intramuscularly induces a fever (38–40°C) within 6 hours that persists for some 4–8 hours. More severe side effects are seen when the drug is administered intravenously, intrathecally, or in patients older than 65 years of age. The use of the highly purified recombinant DNA IFN induces similar side effects. IFN at doses of 50–120 MU results in a sharp febrile response with severe rigors, peripheral cyanosis, vasoconstriction, nausea and vomiting, severe muscle aches, and headaches. In those receiving IFN daily, the febrile response and accompanying symptoms usually decrease in intensity and disappear in 7–10 days. Fever, however, persists with intermittent (nondaily) injections producing a fever that peaks at 6–12 hours and tends to last longer than the normal 4–8 hours. The administration of other biological factors is associated with the onset of fever (e.g., tumor necrosis factor). The administration of growth factors is associated with the onset of fever although the incidence following granulocyte colony-stimulating factor (G-CSF) is very low. Fever occurs much more commonly following granulocyte mac rophage colony-stimulating factor (GM-CSF) administration than with G-CSF administration.

Graft-versus-Host Disease

Chronic graft-versus-host disease is very much like that of a systemic collagen vascular disease and may be associated with infection, with or without the presence of fever. Acute graft-versus-host disease is associated with fever. Infection is also common.

Radiation-Induced Fever

Patients receiving radiotherapy alone may present with fever some hours after the initial treatment. Acute radiation pneumonitis may develop 2–3 months after completion of radiation therapy. A high spiking fever may be part of the syndrome that consists of dyspnea and an unproductive cough. Lung biopsy may be necessary to establish the diagnosis.

Other Diseases

Other diseases that may cause fever may coexist in cancer patients (e.g., systemic lupus erythematosus and rheumatoid arthritis). Careful review of past medical history and current symptoms is essential.

DIAGNOSIS

The classical teaching that history provides 95% of the diagnosis is certainly true when it comes to the symptoms of fever in oncology patients. Following the physical examination, the use of diagnostic aids is related very much to the relevant history. Although two-thirds of neutropenic patients do not have an identifiable cause of their fever, culture of relevant body fluids is still essential. However, routine surveillance cultures in patients with neutropenia, prior to the development of fever, are not cost productive (35). While a CXR may not be indicated in symptomatic patients presenting with febrile neutropenia (36), a recent CXR may be an important baseline in a

patient without respiratory symptoms or signs who is likely to have a prolonged period of neutropenia.

The diagnosis of fever due to the cancer itself can be confirmed with the use of naproxen (37). The proponents of “the naproxen test” state that it does not result in a decrease in temperature in those with infection. The successful treatment of “neoplastic” fever in 21 cancer patients was demonstrated with 15 responding to a dose of 250 mg/ day, while others responded following an increase in the dose of naproxen administered. The true sensitivity and specificity of this test is uncertain, but the authors stress that infectious fever and noninfectious fever due to drug toxicity, allergic reaction, and adrenal insufficiency need to be excluded before considering the diagnosis as “neoplastic fever.”

TREATMENT

Primary to any treatment of fever in cancer patients is the treatment of underlying cause of fever. Antibiotics should not be used to control fever in nonneutropenic patients in the absence of evidence of infection, but nonsteroidal antiinflammatory drugs may be useful in the treatment of fever associated with infection.

Physical cooling (e.g., through sponging) alone is likely to be uncomfortable for febrile patients and should be reserved for those in a hot and humid environment that may impede evaporative heat loss or for those with defective heat loss mechanisms (38). Sponging, when it does take place, should be with tepid water because the use of cold water will induce shivering, which increases patient discomfort and causes an elevation in temperature (39).

Agents that lower body temperature (antipyretics) primarily comprise three groups:

1. Pure antipyretics that do not work in the absence of pyrogen, and at usual therapeutic doses do not affect normal temperature (e.g., acetaminophen)
2. Agents that cause hypothermia in afebrile subjects by directly impairing thermoregulatory function
3. Those that are antipyretic in lower doses and cause hypothermia in higher doses (e.g., chlorpromazine)

Only salicylates, acetaminophen, and ibuprofen have been approved for antipyretic use in the United States, and none of these agents is likely to cause hypothermia in normothermic patients. Aspirin is not recommended for use in children because of the risk of Reye's syndrome, a disease process that results in liver failure (40). Aspirin has been the standard of reference in nearly two-thirds of clinical comparisons of antipyretic activity, but only one comparison of aspirin has been performed in cancer patients (41). Patients with low-grade fever each received doses of aspirin and placebo in random order. No useful conclusions could be drawn, as the mean reduction in temperature for the 600 mg of aspirin was only 0.3°C, not statistically significant from placebo.

In children, acetaminophen has a dose-response effect with doses of 5, 10, and 20 mg/kg bringing about a reduction in temperature of 0.3°C, 1.6°C, and 2.5°C, respectively, after 3 hours (38). Aspirin and acetaminophen appear equally effective at approximately 10 mg/kg. Ibuprofen, 0.5 mg/kg, is about as effective as 10 mg/kg aspirin and 12.5 mg/kg acetaminophen and probably lasts longer. Indomethacin has been reported to be more effective than these three compounds in limiting febrile responses to IFN (42) but is not approved for antipyretic use in the United States. Indomethacin (75 mg), naproxen (500 mg), and diclofenac sodium (75 mg) have been found to be equally effective in the management of paraneoplastic fever (43). Steroids may be useful in treating fever, acting in the same manner as nonsteroidal antiinflammatory drugs. Steroids may be particularly effective in patients who are imminently dying.

Treatment of Infection

The treatment of fever in a nonneutropenic oncology patient is not in itself a medical emergency. Shock associated with such a patient may well make it an emergency. A thorough review of the history and examination and the performance of the appropriate tests should guide both the timing and the type of treatment initiated.

The presence of fever in an immunocompromised patient is a medical emergency and empirical therapy should be initiated as soon as possible. Patients at risk of neutropenia should be instructed to record their temperature and to report the presence of fever to health care staff. An overall schema for the use of antimicrobial agents in neutropenic patients with unexplained fever is presented in Figure 9-3. Antibiotic recommendations by The Infectious Diseases Society of America Consensus Statement on Febrile Neutropenia (44) will be considered together with more recent studies on the choice of antibiotics in febrile neutropenia. The decision as to which antibiotic regimen to use rests with each institution and must take into consideration local experience and infection trends.

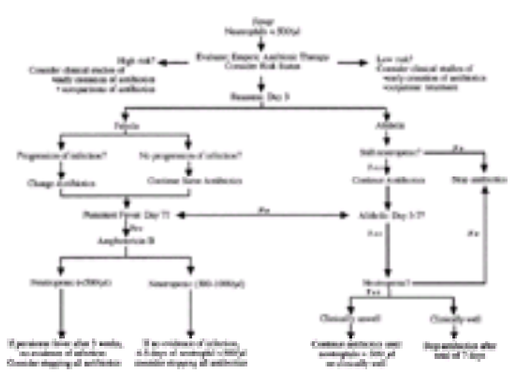

FIGURE 9-3. Clinical approach to the treatment of patients with febrile neutropenia.

The initial choice of antibiotic regimens is most commonly with an aminoglycoside and antipseudomonal beta lactam. These regimes have been extensively used and are particularly recommended for those at high risk of *Pseudomonas* infection, including cancer patients with severe mucositis and those known to be colonized with the organism. Given the nephro- and ototoxicity associated with aminoglycosides, serum concentrations of these drugs should be monitored regularly. Such a two-drug regimen is considered to be as effective as the combination of a third generation cephalosporins with an antipseudomonal beta lactam such as piperacillin. While safe, these latter regimens are expensive, open to resistance, and may not provide adequate coverage of staphylococcal infections. The addition of vancomycin to either of the above regimens provides additional coverage against staphylococcal infections and, if used initially, results in fewer incidences of treatment failure. Other studies have shown no difference in mortality and morbidity rates in those patients in whom vancomycin was added at a later date.

The use of monotherapy was not strongly supported by the committee (44). While initial results of such therapy were good, modification has been required often enough for combination therapy to be preferred as initial therapy. The panel recommended that monotherapy be considered in those at low risk of infection (brief period of neutropenia prior to fever and with neutrophil counts between 500 and 1000/μl) and that these patients be closely monitored. A meta-analysis has subsequently been performed on 13 studies that compared ceftazidime monotherapy with different combination therapies (45). No difference in treatment failure was found, and there was no difference in outcome when febrile and bacteremic episodes were considered independently. Similar percentages of modifications for monotherapy and combination therapy were made. In a more recent multicenter, randomized, controlled trial of the treatment of 876 febrile, neutropenic episodes in 696 patients (46), single-agent ceftazidime was found to be safer than piperacillin and tobramycin combined, while having similar effectiveness (62.7% vs. 61.1%; $p > .2$). Infectious mortality was 6% for ceftazidime and 8% for the combination therapy; 38 episodes of superinfection developed in each group. An adverse event occurred in 8% of the episodes treated with ceftazidime compared with 20% with combination therapy ($p < .001$). Of note, 83% of the patients enrolled in the study were leukemia and transplant patients and often experienced profound and prolonged neutropenia.

The need to continually review a patient's clinical situation and therapy is essential. The consensus panel agreed that by day 3, a neutropenic patient who was either afebrile or had continuing fever but with no progression of the infective process, could continue on the same antibiotics. Antibiotics should be changed if fever persisted and there was progression of the infective process. Either vancomycin could be added at that stage (if not already in use) or monotherapy, in the form of a third-generation cephalosporin, could be commenced. If the patient remained both neutropenic and febrile after a week and was unlikely to have white cell recovery in the near future, amphotericin should be added (47). Antianaerobic therapy should be considered in those with persistent fever and severe oral mucositis, necrotizing gingivitis, or perianal tenderness.

The current duration of antibiotic treatment, where patients with febrile neutropenia have been admitted to hospital for antibiotic treatment until their neutropenia resolved, is based on the results of a 1979 study (48). Early stopping of antibiotics at day 7 in 17 patients with resolved fever but persistent neutropenia resulted in the recurrence of fever in seven patients, of whom two died. The consensus committee considered cessation of antibiotics in afebrile patients who were clinically well but with a neutrophil count of <500/μl. Although not strongly supported by scientific data, they considered that therapy could be stopped after 7 days provided that the

patient was carefully observed, mucous membranes and skin were intact, and no invasive procedures or ablative chemotherapy were imminent.

More recent studies have suggested that in patients at lower risk of complications, outpatient treatment and early stopping of antibiotics may be possible. Thirty febrile neutropenic patients, identified to be of low complication risk after 48 hours of inpatient intravenous treatment, were continued on the same antibiotics at home until neutropenia resolved (49). Four patients were readmitted with medical complications (hypotension, 3; acute renal failure, 1) and five others were readmitted for observation. Overall costs were similar for those treated at home and for those who were medically eligible for home treatment but who were treated in the hospital. The higher-than-expected cost of home treatment related to extended periods of neutropenia in these patients. Attempts have been made to shorten hospital stays by discontinuing intravenous antibiotics in blood culture–negative patients who remained clinically stable and afebrile after 48 hours of treatment (50). In a retrospective review of 134 admissions for neutropenic fever, the median duration of intravenous antibiotics decreased significantly from 7 days prior to institution of such a policy to 5 days (4,5 and 6) and 4 days (3,4 and 5) over the next two consecutive 6-month periods. The median duration of hospital stay decreased from 10 days to 7 days (5,6,7 and 8) and 6 days (5,6 and 7) over the same time periods. The authors concluded that intravenous antibiotics may be discontinued in patients who remain afebrile and clinically stable for 48 hours and who have negative blood cultures, resulting in a shorter duration of hospital stays with the potential for reduction in hospital costs.

Early stopping of antibiotics together with a selective decontamination regimen (neomycin, polymyxin, amphotericin, and pipemidic acid) was prospectively studied in 52 adult patients with hematological malignancies and a neutrophil count <500/µl (51). Patients experienced 77 febrile episodes while receiving the oral antibiotics and further treatment (either broadspectrum or disease-specific antibodies) was initiated only if clinical signs or microbiological culture results indicated an infection. Consequently, antibiotics were adjusted according to culture findings or discontinued if evidence of infection was lacking after 72–96 hours. For the 40 episodes without confirmed infection, the median duration of therapy was 3 days (range, 0–13 days) and the survival rate 100% with 15 receiving no additional antibiotics. For the 37 episodes with confirmed infection, the median duration of therapy was 12 days (range, 1–49 days, p <.0001) and the survival rate 85%. Broad-spectrum therapy was only used for the duration of neutropenia in 18% of the treated episodes, and none of the six deaths could be attributed to the withholding or stopping of broad-spectrum therapy. It was concluded that in febrile neutropenic patients on. this selective decontamination regimen, the standard prolonged administration of broad-spectrum antibiotics was not necessary. The authors recommended for this population that systemic antibiotics be discontinued after 3–5 days if infection is unlikely, that a narrower antibiotic spectrum be chosen according to the clinical situation, and that empirical antifungal treatment be considered after 7 days. Although very promising, the findings of this study need to be confirmed in randomized clinical trials before their widespread implementation.

The place of outpatient treatment of low-risk neutropenic patients was examined at the M. D. Anderson Cancer Center (52). Oral ciprofloxacin combined with clindamycin was as effective in the control of infection as was the combination of intravenous aztreonam and clindamycin. However, the oral regime was associated with increased renal toxicity that resulted in the early termination of the study. The authors recommended the development of better outpatient antibiotic regimens and urged caution as none of their patients had gramnegative bacteremias or pneumonias, a group that may be difficult to treat. Outpatient treatment was further studied in Pakistan, where 188 low-risk patients with febrile neutropenia were randomized to receive either inpatient or outpatient oral ofloxacin (53). The investigators had previously found oral ofloxacin to be as effective for inpatient care as their standard intravenous regimen (54). The patient group consisted of patients with both solid tumors and leukemias and excluded those in whom the duration of neutropenia was likely to exceed 7 days. Fever control was the same in both groups, with 78% of inpatient and 77% of outpatient fevers resolving without modification of the initial treatment. However, 21% of the outpatients required hospitalization. Mortality was 2% in those assigned inpatient treatment and 4% in outpatients, with one death occurring outside of hospital.

The oral administration of empirical, broad-spectrum antibiotics in low-risk patients was tested in a randomized, double-blind, placebo-controlled study of patients who had fever and neutropenia during chemotherapy for cancer (55). Hospitalized patients were randomized to receive either oral ciprofloxacin plus amoxicillin-clavulanate or intravenous ceftazidime. Of 116 episodes in each group, treatment was successful in 71% of episodes in the oral-therapy group and 67% of episodes in the intravenous-therapy group. Concerns have been raised as to the selection of patients in this study. However, this approach may be useful, but it should be limited to that subset of patients with low-risk factors who are not otherwise on quinolone prophylaxis and in whom close monitoring and surveillance can be performed. Those with an identifiable cause of infection should be treated with the appropriate antibiotics. The issue of limited treatment in low-risk groups needs to be more clearly defined and addressed in further clinical studies (Fig. 9-3).

In summary, for patients with fever who continue to have neutropenia for a week or more, broad-spectrum antibiotic therapy for the duration of the neutropenia along with empirical antifungal therapy in those who remain febrile is the current consensus. The use of narrow-spectrum agents or abbreviated courses of antibiotics in these patients is in need of further study as is their role in those patients at low risk of complications.

Vascular access devices often create a treatment dilemma in those with febrile neutropenia. These may be left in place in most patients, even if bacteremia is detected, and managed with antibiotic and local care (56). Catheters should be removed if they are nonpatent, associated with thrombosis, have evidence of septic emboli, or if there is a subcutaneous tunnel infection. Prompt removal of catheters is also indicated with *Candida spp.* fungemia and bacteremia due to *Bacillus spp*. or a bacteremia that persists for >48 hours after initiation of appropriate antibiotics.

Antiviral medications may be required in neutropenic as well as immunocompromised patients without neutropenia. However, the empirical use of antiviral drugs in the management of febrile neutropenia in patients without mucosal lesions or evidence of viral disease is not indicated. The recommended dose of acyclovir for the treatment of established herpes infections in the immunocompromised ranges from 5 mg/kg q8h i.v. for herpes simplex to 10–12 mg/kg q8h i.v. for herpes zoster.

Although popular throughout the 1970s and 1980s, granulocyte infusions use has faded in recent years, despite evidence of efficacy. In a review (57) of the use of granulocyte transfusions, this decline was related to the administration of ineffective doses of granulocytes. The author recommended that physicians assess the outcome of persistent febrile neutropenia in their own institutions and, if poor, the addition of granulocyte transfusions, at therapeutic doses ($2–3 \times 10^{10}$ PMN), may be useful along with other changes such as the use of different antibiotics. The use of G-CSF in the collection of white cells was also considered, but requires more work before its use is considered a standard treatment.

Treatment of Transfusion Reactions

Transfusion reactions can be prevented by filtering of blood products and also by premedication with an antihistamine. The use of erythropoietin in anemia associated with malignancy may reduce the need for blood transfusions, thus avoiding both transfusion reactions and a source of infection. The cost of such treatment needs to be considered carefully.

Treatment of Amphotericin-Related Febrile Reaction

For the prevention of amphotericin-related fever and rigors, 12.5–25.0 mg of intravenous meperidine is useful. However, slowing the rate of amphotericin may reduce toxicity. Amphotericin given over 45 minutes was much more toxic in relation to fever and rigors than the same dose given over 4 hours (58). Less meperidine was required for the control of symptoms in the 4-hour infusion arm. In another study, no difference was found between a 45-minute and 2-hour infusion (59). Other opioids may have the same effect on the treatment of these rigors.

PROPHYLAXIS

Prophylaxis, either in the form of antibiotics or other supportive treatment, may be useful in the prevention of febrile neutropenia.

Growth Factors

Hematological colony-stimulating factors (CSF) reduce treatment-associated myelosuppression by shortening the duration of neutropenia and by reducing the nadir of neutrophil counts. However, concern about their appropriate clinical use lead to the continued updating of guidelines from the American Society of Clinical Oncology (60). These guidelines, initially released in 1994, have resulted in a small improvement in the use of G-CSF (61). Two indications for the use of G-CSF administration were addressed; primary CSF use in those receiving their initial chemotherapy and secondary use in those who have previously had chemotherapy-induced neutropenia.

To assess a benefit in primary prevention, the incidence of Grade 4 neutropenia following CSF use in different randomized treatment protocols was considered. The incidence of neutropenia ranged from 0% in breast cancer patients receiving the combination of cyclophosphamide, doxorubicin, and 5-fluorouracil to 98% of 102 lung cancer patients administered cyclophosphamide, doxorubicin, and etoposide. G-CSF was found to significantly decrease the incidence of febrile neutropenia where the placebo group had an incidence of neutropenia greater than 40%. However, in these randomized CSF trials, no difference in infectious mortality, response rates, or survival between CSF- and placebotreated patients was documented. It was recommended that CSFs only be used with those protocols where the incidence of neutropenia was likely to be greater than 40% without their use. When less myelotoxic chemotherapy is planned, primary administration of CSFs should be reserved for those patients who are at high risk from neutropenic complications because of host- or disease-related factors. Individual cases should also be considered in patients at higher risk of chemotherapy- induced, infectious complications (e.g., extensive prior chemotherapy). Elderly patients tolerate chemotherapy as well as younger patients

and should not receive CSFs purely on the basis of age.

There were few studies concerning the secondary administration of CSFs available to the American Society of Clinical Oncology working group. If a patient has already experienced chemotherapy-induced neutropenia, then CSF can be used if there is proven benefit in maintaining the dose. It is important to remember that for primary use of CSF, there was no difference in infectious mortality, tumor response, or survival. In the absence of a reason to maintain chemotherapy dose, dose reduction should be considered, especially if other toxicities not responsive to CSFs are present. No evidence has been found to support the routine use of CSFs in febrile neutropenic patients, although those at particularly high risk may have some benefit. There has been no evidence to recommend the use of CSFs to increase chemotherapy dose intensity outside of clinical trials addressing this issue. CSFs may be useful for mobilizing peripheral blood stem cells, and they have a benefit in reducing the period of neutropenia in autologous and peripheral blood stem cell transplants. However, there was no indication for their use in patients receiving combined chemotherapy and radiotherapy. When used, the group recommended G-CSF dose of 5 µg/kg/day (GM-CSF, 250 µg/m^2/day), without dose escalation, administered 24–72 hours after chemotherapy until the neutrophil count is greater than 10,000/µl after the neutrophil nadir.

The implications, including cost, of the use of G-CSF in the treatment of small cell lung cancer at the University of Indiana were reviewed (62). The overall incidence of neutropenia was 18% in the 137 patients treated with standard chemotherapy and in whom dose reductions were allowed on subsequent courses. The estimated total cost of this treatment was approximated to be $192,000. There would have been more than a six-fold increase in cost ($1,200,000) if primary treatment of all patients with G-CSF had taken place. The cost of the secondary use of G-CSF in those with a previous episode of fever and neutropenia ($272,000) would have been less than twice that of not using growth factors at all. The authors concluded that the routine use of G-CSF in small cell lung cancer patients treated with standarddose chemotherapy was expensive and not associated with obvious therapeutic benefits or cost savings. They suggested that careful analysis of the incidence of infectious complications, rather than granulocyte nadir and duration, be performed.

Other Prophylactic Measures

Although total protected environments (involving laminar flow, the oral administration of nonabsorbable antibiotic, and cutaneous decontamination) reduce the incidence of infection, their use proved cumbersome and expensive, and they have largely been abandoned (18), particularly for those patients for whom the duration of neutropenia is likely to be short. Individual components of these regimens, however, continue to be used in many treatment protocols.

There have been mixed results from the oral administration of nonabsorbable drugs such as gentamycin, nystatin, and van comycin. The consensus panel could make no recommendation as to use of the drugs but agreed strongly that the use of aminoglycosides in this situation should be avoided. In a recent review, the use of nonabsorbable antibiotics without concurrent patient isolation was not recommended because of the unpalatability of the antibiotics, their cost, the emergence of resistant organisms, and the lack of constant efficacy (18).

The Infectious Diseases Consensus panel (44) recommended trimethoprim-sulfamethoxazole prophylaxis for afebrile, uninfected patients with profound neutropenia expected to persist for at least 1 week. This combination has a role in the prevention of *Pneumocystis* infections in transplant patients and has been used in protocols such as MACOP-B. Norfloxacin, an oral quinolone, has been found to reduce gramnegative infection when compared with Bactrim, but the possibility of the development of resistance prevented the Consensus group from recommending its routine use. The role of prophylactic ciprofloxacin in reducing the incidence of neutropenic fever in 88 consecutive men receiving intensive chemotherapy for germ cell tumors was reviewed. In total, 88 men received 429 courses of chemotherapy and prophylactic ciprofloxacin was prescribed for 168 courses. The incidence of fever in these patients was significantly reduced from 15% (20/131) to 5% (6/109) (p =.02) with prophylactic ciprofloxacin. Two patients, one of whom had received prophylactic ciprofloxacin, died of chest infections confirmed on postmortem. The results of this nonrandomized, retrospective study suggest that prophylactic ciprofloxacin, 250 mg twice a day, is effective in reducing the incidence of fever complicating neutropenia during chemotherapy for germ cell tumors. To be cost effective, however, it should be given only to neutropenic patients (63). Ciprofloxacin (750 mg twice a day) was found to be as safe and effective as trimethoprim-sulfamethoxazole (160 mg/800 mg twice a day) in the prevention of bacterial infections in 146 bone marrow transplant patients. However, ciprofloxacin was associated with a lower incidence of C. *difficile* enterocolitis and infections caused by gramnegative bacilli, indicating an advantage for its use in transplant patients (64). Prophylaxis also extends to antiviral medications. Acyclovir use decreases the incidence of herpetic gingivostomatitis in patients with neutropenia, and the administration of acyclovir decreases the incidence of cytomegalovirus pneumonitis in patients who have undergone bone marrow transplant.

ETHICAL CONSIDERATIONS OF TREATMENT OF INFECTIONS

There is no doubt that if the intention of treatment is to ensure the prolongation of survival, then treatment of the infective episode needs to be initiated. Dilemmas may arise in those patients in whom the intention of treatment is palliation. Antibiotics may make a patient feel more comfortable, but they may also prolong the dying process. A balance between the two should be assessed in each individual patient, factoring in particular factors such as prognosis and treatment goals.

Even if a patient is nearing death, indications for commencement of antibiotics may include convulsions or mental changes attributed to fever, extreme temperature (>40°C), extreme age (very young and very old), and a past history of adverse reaction to fever, marked subjective discomfort pronounced by patient, a prolonged high fever causing significant hypercatabolic state, and a reduced cardiac or pulmonary function to the extent that further tachycardia or tachypnea may be harmful. Further issues pertaining to this will be discussed in other chapters.

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10

ANOREXIA/WEIGHT LOSS

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Loss of weight and appetite predict a poor prognosis for cancer patients and spawn anguish for patients and their families. The Latin aphorism, *optimum condimentum fames* (“hunger's the best sauce”) alludes to hunger's reliability as an indicator of health and, at the same time, implies that unintentional loss of weight and appetite are associated with unfavorable health outcomes (1). Multiple clinical investigations have demonstrated that this adverse sign and symptom serves as a powerful predictive instrument in patients with cancer.

In the largest of these clinical investigations, DeWys and others retrospectively examined the records of 3047 cancer patients from 12 different Eastern Cooperative Oncology Group (ECOG) chemotherapy clinical trials (2). Patients had been evaluated for weight loss before trial participation. Loss of more than 5% of premorbid weight predicted a poor prognosis among patients with a variety of different tumor types, including lung cancer, breast cancer, gastrointestinal malignancies, and lymphoma. Even after adjusting for performance status, a strong association between weight loss and an early demise persisted. Weight loss was also associated with a trend towards lower chemotherapy response rates. Other large studies, including those that have used treatment modalities other than chemotherapy, also demonstrate a direct association between loss of weight and shortened survival (3,4). Along similar lines, but focusing on appetite, Chang recently reviewed the prognostic effect of this adverse symptom among cancer patients (5). He summarized several studies, including a multivariate analysis from the North Central Cancer Treatment Group, which examined patients with lung and gastrointestinal malignancies with a focus on physiological and psychological factors that might effect prognosis (6). A large number of these studies demonstrate that appetite loss also predicts a poor prognosis for cancer patients, thus adding to a growing body of literature that underscores this strong relationship between compromised nutritional status and an early demise.

The emotional impact of cancer-associated weight loss and anorexia may be just as strong as their negative prognostic impact. Peteet and others characterize this emotional impact in a paper entitled “Psychological Aspects of Artificial Feeding in Cancer Patients.” Relying on a series of case reports from which to draw conclusions on the psychological toll exacted by cancer-associated weight loss and anorexia, these investigators provide the following insights (7):

> For many, loss of appetite, weight, and body image are primary means by which cancer threatens their sense of self and autonomy. Inability to eat is often experienced as a failure of will. Similarly, for many families, feeding is a means of giving and caring, so that a patient's acceptance or rejection of food, especially in a time of family crisis, has pervasive implications for family relationships. Finally, for many persons, cachexia is closely associated with death from cancer, and with maintenance of health.

Such conclusions draw attention to the insidious but farreaching consequences of cancer-associated weight loss and anorexia.

Combining the above data on prognosis and emotional impact with studies on prevalence further enlarges the magnitude of the mortality and morbidity of cancer-associated anorexia and weight loss. In an ambulatory care setting, Tchekmedyian and others found that among 644 consecutive patients, approximately half had anorexia or weight loss of greater than 5% of premorbid weight (8). In a comprehensive prospective analysis of 1000 patients with advanced cancer about to enter a Hospice program, Walsh and others. found that 66% were experiencing anorexia (9). These prevalence rates might well become higher if gathered during the very final stages of life.

PATHOPHYSIOLOGY

Why are cancer-associated weight loss and anorexia associated with such devastating outcomes? The answer might rest in a more detailed understanding of events at the tissue level. Cancer patients who are losing weight waste both fat and lean tissue. With respect to loss of adipose tissue, many weight-losing cancer patients manifest a constellation of hyperglycemia, hypertriglyceridemia, and an exaggerated insulin response to glucose intake. Wasting of adipose tissue appears to be mediated by a lipid-mobilizing factor from the tumor (10). What is most striking about this wasting of body tissues, however, occurs within the lean tissue compartment. An excessive loss of lean tissue is a hallmark of cancer-associated weight loss and is not generally observed in other, more commonly discussed clinical settings (e.g., simple starvation). Cohn and others assessed body composition with tritiated water, prompt gamma neutron activation, and total body potassium among 50 cancer patients (11). They went on to make direct comparisons to age- and sex-matched controls. In contrast to the control group, weight-losing cancer patients manifested a dramatic loss of lean body tissue, most notably of skeletal muscle. Although this study did not include a direct comparison to starving but otherwise healthy controls, this pattern of lean tissue wasting stands in contrast to the relative preservation of lean tissue observed in starvation (12), in which lean tissue is relatively preserved, although the adipose compartment withers.

This phenomenon of lean tissue wasting carries grave potential consequences. Previous studies have observed that loss of weight and loss of performance status go hand-in-hand in cancer patients. In the study by DeWys and others, patients were also segregated by ECOG performance status (2). Patients with a worse performance status of 2–4, compared to a better performance status of 0–1, had higher rates of weight loss ($p < .01$ among 9 of 12 tumor types). In yet another ECOG study, Finkelstein and others found that a loss of >5% of premorbid weight was associated with greater debility (13). Thus, as cancer patients lose weight, they tend to manifest a decline in their ability to care for themselves and perform activities they formerly enjoyed. Furthermore, if we acknowledge that the lean tissue body compartment carries all the body's metabolic machinery, it becomes plausible that vital functions, such as respiration, blood circulation, bowel function, cognition, and ambulation, might become compromised when this body compartment erodes. It also becomes within grasp to speculate that weight loss—by means of lean tissue wasting—may in fact bear a cause and effect relationship when it comes to death from cancer. Early autopsy studies in patients with advanced cancer are often quoted to bolster this speculative cause and effect relationship: Anywhere between 1% and 20% of cancer patients had no discernible immediate cause of death other than “cachexia” at the time of their postmortem examination (14).

Because of these potential implications, recent studies have focused on identifying mediators of lean tissue wasting. Todorov and others have discovered a 24-kd proteoglycan from a tumor homogenate from the MAC16 tumor line (15) and have named this substance *proteolysis-inducing factor* (PIF). PIF appears to have direct proteolytic activity on muscle, and PIF antibodies prevent weight loss in animal models if given before PIF administration. Discovered in the urine of weight-losing cancer patients but not in the urine of weight-stable cancer patients or weight-losing noncancer patients, PIF also appears to be quite specific for cancer-associated wasting. In addition to this purported mediator of cancer-associated wasting, other mediators that appear to play an active role the syndrome of cancer-associated anorexia and weight loss include TNF-a, IL-b, IL-6, and ciliary neurotrophic factor (16,17,18,19,20 and 21). Previous animal studies have identified such cytokines in the setting of cancer-associated weight loss and have observed attenuation of cancer-associated anorexia and weight loss with administration of antibodies to these cytokines. Elucidating a potential pathway that might lead to muscle wasting in the cancer setting, Guttridge and others recently found that TNF-a's activation of NF-kappaB suppresses MyoD, a factor that is normally active in muscle repair (22). Although these investigators had not specifically examined cancer-associated wasting, identical or parallel mechanisms might ultimately prove responsible for the erosion of muscle tissue observed in cancer patients. Finally, several studies have implicated the ubiquitin-proteasome pathway in lean tissue wasting and have suggested that this pathway leads to wasting of muscle and perhaps other components of lean tissue in cancer (23,24). Baracos and others have suggested that the ubiquitin proteasome pathway might be responsible for as much as 80% of the muscle degradation that occurs in cancer-associated wasting (25).

In addition to direct erosion of lean tissue, other events perturb the balance of energy in cancer patients and predispose to weight loss. First, an increase in resting energy expenditure contributes to energy deficits. Elevations in resting energy expenditure have been observed in patients with lung cancer (even nonmetastatic non-small cell lung cancer) (26), hematological malignancies, and sarcomas (27,28,29 and 30). Gastrointestinal malignancies do not appear to predispose to this hypermetabolic effect. Although some investigators have suggested that this hypermetabolism may arise from underlying comorbidities such as ongoing infections or chronic obstructive pulmonary disease, many studies suggest that some cancers contribute single-handedly to this increase in metabolic rate. Recent studies have invoked uncoupling proteins as contributing to these metabolic aberrations. For example, Bing and others found that con centrations of mRNA for uncoupling protein-1

(UCP-1) were significantly increased in brown adipose tissue in a murine tumor model (31).

Second, previous studies suggest that cancer patients eat less. Theologides and others studied 39 cancer patients, 18 of whom had lost more than 10% of their body weight (32). Concurrently, all these patients reported a drop in their food intake of at least 300 kcal/day. This pioneering pilot study provides data to substantiate the hypothesis that amidst all the metabolic mayhem that occurs in the tumorbearing host, weight-losing cancer patients are, in fact, eating less. The etiology of this diminished food intake is multifactorial and might include cytokine-mediated anorexia, altered taste and nausea from antineoplastic treatment, depression, acquired food aversions, and compromised access to food due to increasing debility or hospitalization.

TREATMENT OPTIONS

Role of Caloric Supplementation

Caloric repletion might seem to be the most reasonable approach to the treatment of cancer-associated weight loss. As already discussed, in the setting of cancer, the host is plagued by energy deficits that arise from an increase in resting metabolism and poor oral intake. Hence, nutritional support, either in the form of enteral or parenteral nutrition, might compensate for such deficits. However, in advanced cancer patients, caloric supplementation rarely helps. For example, trials that have examined dietary counseling in chemotherapy patients with advanced cancer have not demonstrated favorable outcomes. Ovesen and others evaluated 105 patients who were being treated with chemotherapy for cancer (33). These investigators randomly assigned patients to receive either nutritional counseling or no nutritional counseling. Patients who received nutritional counseling consumed significantly more calories. However, direct comparisons between the two groups to assess outcomes such as tumor response rates, survival, and quality of life demonstrated no differences. Other, more aggressive measures aimed at caloric repletion have also been disappointing. A review of clinical trials that examined total parenteral nutrition in cancer patients with advanced disease led the American College of Physicians to issue a consensus statement in 1989 discouraging its use in patients undergoing chemotherapy (34). These recommendations remain unrevised today.

Although nutritional support—either in the form of parenteral or enteral nutrition—is generally discouraged in cancer patients, previous studies suggest a few circumstances in which its use can be justified. These include the following: (a) in patients undergoing stem cell or bone marrow transplantation; (b) perioperatively; and (c) during treatment for head and neck cancer. Studies that support the use of nutritional support in these settings, however, must be viewed in the context of other clinical trials, which have not shown clinical benefit with the use of parenteral nutrition.

First, nutritional support potentially may help patients in the setting of stem cell rescue after highdose chemotherapy. Weisdorf and others performed one of the earlier studies examining total parenteral nutrition in a study population of 137 patients, most of whom (93%) had cancer—mainly, acute leukemia (35). These investigators randomly assigned patients to receive either total parenteral nutrition or intravenous fluids, which consisted of a 5% dextrose solution. The majority of patients in the control arm crossed over to receive total parenteral nutrition because of malnutrition. Nonetheless, direct comparisons between the two study arms demonstrated that a number of clinical outcomes, including overall survival, were improved in patients initially assigned to the total parenteral nutrition arm. Although some might argue that transplantation has changed over the past decade to the point where patients engraft more quickly and are therefore less vulnerable to developing malnutrition, this study suggests that total parenteral nutrition might confer benefit when administered prophylactically.

Second, two studies suggest perioperative nutrition might benefit severely malnourished cancer patients. The first study is the Veteran Affairs Total Parenteral Nutrition Cooperative Group Trial, which examined 395 malnourished patients (36). Although not all of these patients had cancer, 65% did. Patients were randomly assigned to receive at least 7 days of total parenteral nutrition or no total parenteral nutrition. Twenty-four of these 395 patients were severely malnourished, as defined by their Nutrition Risk Index, a reasonable instrument designed to assess nutritional status. It was within this small subgroup that clinical benefit with total parenteral nutrition was observed. This subgroup manifested fewer noninfectious complications—such as anastomotic leak, bronchopleural fistula, and others—when compared to severely malnourished patients who did not receive nutrition support.

Before totally accepting the conclusions of this trial at face value, however, some aspects of the trial design merit discussion. The trial has been criticized because it included patients with mild to moderate malnutrition, and some nutritionists contend that only patients with severe malnutrition should have been included. It is important to point out, however, that these investigators had carried out subanalyses to examine potential differences between groups, and that these subanalyses had been planned *a priori* with respect to the trial's initiation. Admittedly, the conclusions of this trial would have been more compelling had the number of severely malnourished patients exceeded 24, but this small number speaks to the fact that relatively few severely malnourished patients are surgical candidates in the first place. Another concern is the lack of double-blinding. A valid criticism, this shortcoming is also difficult to surmount. Complete double-blinding when prescribing total parenteral nutrition administration is problematic, especially when one considers the metabolic aberrations, including hyperglycemia and electrolyte abnormalities, which must be managed. Working within such practical constraints, this study provides reasonable justification for administering total parenteral nutrition to severely malnourished patients immediately before surgery.

Couple the results of the Veteran Affairs Total Parenteral Nutrition Cooperative Group trial with the results of a trial by Fan and others (37), and one acquires further justification for considering total parenteral nutrition in severely malnourished patients in the perioperative setting. Fan and others studied 124 malnourished patients with hepatocellular carcinoma before surgery. Many of these patients were touted as being only mildly malnourished, as suggested by the fact that only 20% had sustained a loss of >10% of their premorbid weight; however, in the setting of liver disease, evidence of malnutrition can be occult. In this placebocontrolled trial, patients who were randomly assigned to receive total parenteral nutrition also experienced a decrease in postoperative morbidity and a reduction in the use of diuretics after surgery. However, similar to the Veteran Affairs Total Parenteral Nutrition Cooperative Group trial, a survival advantage with the use of total parenteral nutrition was not seen in this study.

Finally, although head and neck cancer patients may also benefit from nutritional supplementation, study results are far less convincing than the other two indications cited previously. Two small studies suggest that enteral feeding may lead to fewer treatment delays in patients receiving radiation for head and neck cancer and may improve functional ability several months after completion of therapy (38,39). Although these data are in large part exploratory in nature, they nonetheless provide some justification for aggressive oral nutrition in head and neck cancer patients during aggressive antineoplastic treatment.

Because not all groups of cancer patients have been formally studied with respect to implementation of adjunctive nutrition therapy, how do we decide when to use it? In our own medical oncology practice, we find that we use nutritional support sparingly, if not rarely. However, outside of the clinical settings discussed previously, one might be able to justify its use if patients meet both of the following criteria: (a) notably malnourished or at risk for becoming so during cancer treatment; and (b) diagnosed with a potentially curable malignancy or about to receive cancer treatment that may result in a long diseasefree period. Otherwise, in patients with advanced incurable cancer, there is no substantial justification for prescribing enteral or parenteral nutrition.

Patients with Advanced Incurable Cancer

To date, the most effective approach for treating cancer-associated anorexia and weight loss revolves around palliating anorexia. Several clinical trials have been unable to demonstrate survival advantages or improvement in global quality of life even with the use of state-of-the-art interventions aimed at palliating anorexia. Nonetheless, because dying cancer patients rank anorexia as their third most noxious symptom (9), an argument can be made for attempting to palliate it. In our own practice, we use a two-step approach before the initiation of orexigenic agents (Fig. 10-1). The first step involves predicting whether a patient is likely to receive palliation of anorexia as a result of antineoplastic therapy. A recent study by Geels and others underscores the importance of attempting to predict tumor response before treating anorexia with other maneuvers (40). These investigators assessed 300 patients who were about to receive chemotherapy for breast cancer. They found that 82% of patients who demonstrated a partial or complete response to therapy also manifested an improvement in anorexia. Thus, if a patient is likely to obtain tumor regression with antineoplastic treatment, we often forego other palliative measures to help with anorexia, saving them for later. The second step involves a frank discussion with patients and family members about eating goals. As pointed out earlier by Peteet and others, guilt often accompanies loss of appetite (7). If mealtime represents a time of “giving and caring,” then the cancer patient's inability to eat carries with it a mixture of failure and frustration for both the patient and family. We talk with patients and families about realistic expectations during meals and explain some of the reasons behind compromised oral intake in the cancer setting. After such discussions, patients and family members usually become more accepting of loss of appetite. If pharmacological manipulation of appetite is desired, they better understand the goals behind its use.

FIGURE 10-1. Algorithm of advanced cancer patient with loss of appetite.

A subgroup of patients ultimately opts for drug therapy to improve appetite. In sifting through the published literature to decide on the best agent to try, it is important to consider certain elements of clinical trial design that make clinical investigation in this field especially challenging. First, earlier studies have described a significant placebo effect, which may be as high as 40% with oral agents (41). It is conceivable that placebos administered by intravenous or subcutaneous methods may carry even higher response rates, as demonstrated by clinical studies in the noncancer setting (42). In view of such high "response rates" with placebo alone, it is important to evaluate phase II trials in cancer-associated anorexia with caution and to maintain placebo-controlled trials as the gold standard for efficacy. Second, because patients with advanced cancer and anorexia are ill, dropout rates in these trials are high. A common pitfall is to ignore dropouts and conclude that one treatment arm is more efficacious than another on the basis of a group of biased survivors. Although circumventing this pitfall is challenging, successful strategies include planning for large sample sizes and carefully stratifying patients on the basis of well-defined prognostic criteria. It is also important to include short but frequent assessments of appetite early in the trial to capture differences between study groups before the onset of further morbidity.

When such criteria are applied to "promising" agents, most are found to be no better than placebo, or even inferior to another agent. So-called "promising" agents that have fared well in pilot studies but not in large controlled trials include hydrazine sulfate, anabolic steroids, pentoxifylline, dronabinol, and cyproheptadine hydrochloride. First, because hydrazine sulfate inhibits gluconeogenesis, it seemed a reasonable choice for further clinical study among cancer patients with weight loss. However, at least two large clinical trials in cancer patients have shown that this agent is not effective in this setting (43,44). Moreover, hydrazine sulfate is associated with toxicity, and a fatal case report was recently published (45). Second, with respect to anabolic steroids, a recent trial by the North Central Cancer Treatment Group found that the androgen fluoxymesterone resulted in lower rates of weight gain than megestrol acetate or dexamethasone in patients with cancer-associated loss of appetite and weight (46). Third, pentoxifylline is a methylxanthine derivative that is thought to inhibit the production of TNF-a. Based on this purported mechanism, the North Central Cancer Treatment Group launched a randomized, placebo-controlled trial among patients with cancer-associated loss of appetite and weight, but found that this agent resulted in no improvement in either appetite or weight among this group of patients (47). Fourth, dronabinol has been touted as an effective agent for boosting appetite among AIDS patients, and placebo-controlled trials support its use in the setting of AIDS-related loss of appetite (48,49). However, a recently completed trial by the North Central Cancer Treatment Group did not find a similar effect among cancer patients (50). In the latter study, 469 evaluable cancer patients with loss of appetite or weight were randomly assigned to receive either megestrol acetate with placebo, dronabinol with placebo, or combination therapy. Megestrol acetate proved superior to dronabinol as an orexigenic agent, and combination therapy added nothing above and beyond megestrol acetate alone. Hence, there appears to be little role for dronabinol, as prescribed in this study, for the treatment of cancer-associated loss of appetite. Fifth, cyproheptadine hydrochloride, a histamine and serotonin antagonist, was also evaluated in a large placebocontrolled trial and was found to carry only minimal appetite stimulatory effects (51). In summary, these agents have, at best, limited use in the management of cancer-associated anorexia.

In contrast, two other classes of agents have proven themselves effective: progestational agents and corticosteroids. Both medroxyprogesterone acetate and megestrol acetate have been demonstrated to improve appetite in patients with cancer-associated anorexia; the latter having been more extensively studied. To our knowledge, 13 of 15 placebo-controlled trials have been published demonstrating that megestrol acetate improves appetite in the cancer setting (52). Despite these favorable orexigenic effects, however, it is important to underscore that this agent has not been shown to augment lean tissue, to improve global quality of life, or to advance survival. A direct dose–response effect occurs between megestrol acetate and appetite stimulation; this effect generally reaches a plateau at doses of beyond 800 mg/day (53). Because the oral suspension formulation carries better bioavailability, we normally begin with this formulation at a dose of 400 mg/day and increase to 600–800 mg/day over 2–4 weeks, should patients fail to derive an orexigenic effect. However, in the event that patients suffer a serious infection or trauma, we prescribe supplemental corticosteroids because of the potential for adrenal axis suppression.

Corticosteroids also work (54). Loprinzi and others recently compared megestrol acetate, dexamethasone, and fluoxymesterone for the treatment of cancer-associated anorexia (46). Although the anabolic agent, fluoxymesterone, was not effective, the other two agents were relatively comparable in efficacy at the doses prescribed. Dexamethasone, however, was associated with a worse side effect profile; for this reason, we recommend dexamethasone for cancer patients with a less favorable prognosis, because troublesome side effects such as myopathy are unlikely to occur in the short term. Dexamethasone is also a reasonable choice in patients at higher risk for thromboembolic phenomena and in those who require a less expensive orexigenic agent. Megestrol acetate is a reasonable choice for most other cancer patients who choose to try an orexigenic agent for anorexia.

New Agents

Thalidomide is a newly described appetite stimulant that deserves further investigation in this setting. A suppressor of TNF-a, thalidomide shows promise in phase II trials as a potential appetite stimulant and weight stabilizer among cancer patients. To our knowledge, phase III studies to investigate the primary end points of appetite, weight, or body composition have not been published in cancer patients. However, two phase II studies suggest that this agent should be further investigated (55,56). Eisen and others administered thalidomide, 100 mg/day orally, to 66 cancer patients. Although only three patients manifested tumor regression, 14 of 15 who completed quality of life questionnaires noted either stability or improvement in appetite. Similarly, Boasberg and others recently studied 15 weight-losing patients with metastatic cancer. They prescribed thalidomide, 100 mg p.o. q.h.s., but escalated the dose to 200 mg p.o. q.h.s. if treatment was well tolerated. Patients appeared to stabilize their weight. Of note, dose was an important aspect of both these trials. Whereas earlier thalidomide trials had administered high doses of thalidomide with high toxicity rates and severe toxicity grades, this regimen of continuous, relatively low-dose thalidomide appeared to be well tolerated, thus laying the groundwork for further investigation of this agent in this setting.

Adenosine triphosphate (ATP) also shows promise. Using this key energy source, Agteresch and others tried to attack the phenomenon of hypermetabolism in non–small cell lung cancer patients and advanced the hypothesis that ATP may attenuate weight loss. These investigators randomly assigned metastatic non-small cell lung cancer patients to ATP versus no ATP (57). Dropout rates in this study were high, which may have created selection bias between groups at the time of data analysis. Nonetheless, the ATP-treated group maintained weight and showed evidence of improved appetite in contrast to the control group. Because ATP requires intravenous administration, it may represent a cumbersome approach to a debilitating clinical problem. At the same time, however, these preliminary data suggest potential efficacy in the treatment of both anorexia and tissue wasting and suggest a need for further clinical investigation.

An omega-3 fatty acid derived from fish oil, EPA, appears to attenuate cancer-associated tissue wasting in preliminary clinical trials (58,59). Barber and others studied 20 patients with unresectable pancreatic cancer. All of these patients were losing weight, but after starting fish oil supplements, which contained 1.09 g of EPA, weight gain was observed over several weeks. Gogos and others studied 60 patients with advanced cancer in a placebo-controlled trial, which administered a fish oil–based supplement versus placebo (60). A slight survival advantage was observed in the group that received the supplement. Hussey and Tisdale and others suggest weight-sustaining mechanisms that may be at work. In an animal study, these investigators suggest that EPA may suppress PIF (61). An ongoing North Central Cancer Treatment Group is examining EPA versus megestrol acetate versus a combination of both agents to compare the effects of these treatments on appetite, weight, and body composition in patients with advanced cancer who have anorexia or weight loss.

Intriguing information has also been reported for ondansetron, a type 3 serotonergic receptor antagonist. This agent's remarkable ability to treat chemotherapy-induced nausea and vomiting has fostered interest in its potential role in the treatment of cancer-associated anorexia. In a phase II trial that examined 27 patients with advanced cancer and weight loss, Edelman and others prescribed ondansetron 8 mg twice a day (62). Patients were not receiving antineoplastic treatment. Although 20 evaluable patients continued to lose weight, appetite assessment with a 7-point hedonic scale suggested patients were enjoying food more after 1 month: 5.15 ± 0.9 compared to 5.49 ± 0.32 at baseline and 4 weeks, respectively (mean score ± standard error of the mean; $p = .04$). A large, placebo-controlled trial might clarify whether these promising results represent a true orexigenic effect.

Melatonin is another agent that has preliminary positive results for treatment of cancer-associated anorexia or weight loss. In a trial of 100 patients with metastatic cancer, Lissoni and others found that melatonin at an oral dose of 20 mg/day resulted in a significantly lower rate of weight loss when compared to placebo-treated patients (63). Mechanisms by which this agent might be working remain unknown, and confirmatory trials are necessary.

Because many mediators of cancer-associated weight loss, such as TNF-a, IL-b, and IL-6, also mediate inflammation, some clinical trials have focused on the use of nonsteroidal antiinflammatory agents. Cahlin and others found that tumor-bearing mice increased their food intake with indomethacin (64). In addition, mice with a genetic knockout of IL-6 ate more with indomethacin. Several small clinical studies suggest that ibuprofen abrogates the inflammatory response and results in modest weight gain (65,66). In contrast to these favorable results, however, McCarthy treated tumor-bearing mice with indomethacin but observed no improvement from a nutritional perspective (67). Thus, the role of nonsteroidal antiinflammatory agents in weight-losing cancer patients needs to be better defined.

Our improved understanding of some of the mechanisms that conspire to create this syndrome of cancer-associated anorexia and weight loss has recently led to some particularly novel approaches. The relationship between NF-kappaB and the upregulation of TNF-a, a cytokine implicated in cancer-associated anorexia and weight loss, was recently exploited by Kawamura and others (68). Having developed a double-stranded oligodeoxynucleotide that configured the ciselements of NF-kappaB, these investigators hypothesized that direct injection of this decoy into tumors would attenuate anorexia and weight loss. Tumor-bearing mice that received the decoy did not develop tumor regression, but there did appear to be a trend suggestive of increased food intake and weight stabilization. In contrast, tumor-bearing mice that received a scrambled decoy demonstrated a rapid nutritional decline. Results such as these require confirmation and suggest that this novel approach merits further investigation.

Along similar lines, Torelli and others explored the use of a dimeric, pegylated 55-kDa TNF receptor construct for purposes of palliating cancer-associated anorexia (69). These investigators used an animal model to test their hypothesis that TNF-a blockade would attenuate anorexia in this setting. Direct comparisons between animals that received this TNF-a inhibitor and those that received only vehicle demonstrated that cytokine blockade resulted in improved ad libitum food consumption. This effect appeared sustained over 8 days. Thus, this study, in addition to some of those cited above, suggests that TNF-a might be a worthwhile treatment target for cancer-associated anorexia and weight loss.

CONCLUSIONS

Recent novel therapies have generated new enthusiasm for tackling the frustrating but common problems of cancer-associated anorexia and weight loss. The mainstay of management continues to be a combination of counseling, appetite stimulants such as progestational agents and corticosteroids, and occasionally, nutritional support. However, our improved understanding of the pathophysiology of this syndrome has led to targeted therapies aimed at not only improving appetite but also augmenting lean tissue.

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11

ORAL SENSATION AND CANCER

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Food has an immense impact on our quality of life. Eating, as with the preparation of meals, is often a social activity, and the consistent flavor of packaged cookies or a family recipe subtly reminds us of the few constants in our lives. It stands to reason, then, that changes in the food we know can have a profound effect on us, especially if they arrive at a particularly stressful time (e.g., after a cancer diagnosis or while undergoing treatment). Changes in a cancer patient's relationship to food can influence response to treatment: Diminishing appetite and multiplying aversions to necessary nourishment can compromise a patient's strength, morale, and chances of survival. This chapter aims to familiarize clinicians with the chemosensory mechanisms responsible for the perception of foods and beverages and the causes of dysfunction in these mechanisms. It also reviews reports associated with cancer and its related therapies. This helps the clinician determine whether a patient complaint represents an alteration in sensation per se or an alteration in the pleasure associated with eating food.

ORAL SENSATION: A REVIEW OF FUNCTION

Foods and beverages are perceived as a complex mixture of true taste, smell, and oral somatosensory (touch, temperature, and pain) sensations. These sensations function through separate neural pathways yet are tightly integrated to provide the composite sensation of food flavor. Alteration of one or more of these sensations can alter the composite flavor sensation, leading to an abnormal sensory experience and diminished enjoyment of eating.

True taste involves perceiving substances that impart salt, sweet, sour, and bitter sensations. Taste buds, clusters of receptor cells containing receptor sites for these compounds, are present on specific regions on the tongue, between the hard and soft palate and in the throat (Fig. 11-1). The elongated tips of the receptor cells contain taste receptor sites. These tips project into a space (taste pore) in which they come into contact with taste stimuli. On the tongue, taste buds are found in papillae. The fungiform papillae (which resemble small button mushrooms) are most densely distributed on the tip and edges of the tongue. The foliate papillae are on the edges at the base of the tongue. and the circumvallate papillae are circular structures arranged in an inverted V across the base of the tongue. Three cranial nerves innervate taste buds and route taste information to the medulla, the ventrobasal thalamus, and finally, to the cortex. The facial nerve VII innervates taste buds in the fungiform papilla through the chorda tympani branch and innervates taste buds on the palate through the greater superficial petrosal branch; the glos-sopharyngeal nerve IX innervates foliate (these may also be innervated by cranial nerve VII) and vallate papillae on the posterior tongue; and the vagus nerve X innervates taste buds in the throat. Incidentally, the taste map of our high school textbooks showing sweet perceived on the tip of the tongue, bitter on the back, etc., is incorrect; it stems from the mistranslation of a German thesis. In reality, all four taste qualities can be perceived on all areas of the tongue and palate in which there are taste buds (1).

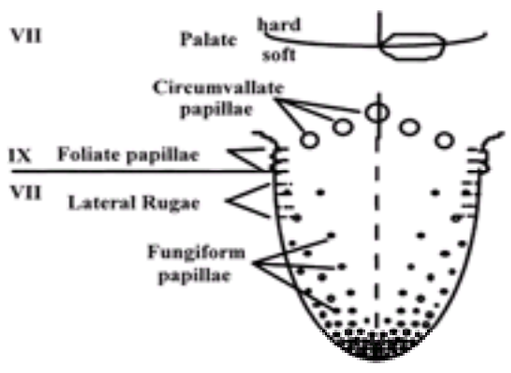

FIGURE 11-1. Drawing showing areas of cranial nerve innervation to taste buds within papillae on the tongue and to taste buds in between the hard and soft palate.

The sense of smell serves as a dual sensory system: We experience the aroma of foods through the nostrils and a substantial component of food flavor through the mouth (Fig. 11-2). Smelling through our nostrils can be passive, as when we breathe, or active, as when we concentrate odors by sniffing (i.e., orthonasal olfaction). Air enters the nostrils and moves up past the turbinate bones. A small sample of this air ultimately reaches the top of the nasal cavity, travels through a small opening called the olfactory cleft, and then contacts the olfactory receptors (located behind the bridge of the nose). The receptors for olfaction are found on the ciliated dendrites of olfactory fibers. Odors can also reach the olfactory receptors from the mouth, where active chewing and swallowing create a pressure gradient and push air from the mouth up behind the palate into the nose (retronasal olfaction). Whether orthonasal or retronasal in origin, once an odor reaches the olfactory receptors, it is carried by the olfactory nerve (cranial nerve I) through the cribriform plate to be distributed to the olfactory bulb.

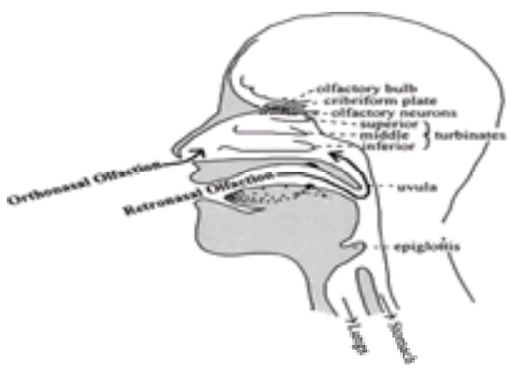

FIGURE 11-2. Drawing showing the two pathways to olfactory perception. Orthonasal olfaction occurs passively as we breathe, and retronasal olfaction occurs actively through mouth, tongue, and throat actions. Both pathways carry odors to olfactory receptors that sit behind the bridge of the nose.

Touch, temperature, and irritation or pain sensations from eating are mediated by the lingual branch of the trigeminal nerve on the anterior tongue and by the glossopharyngeal nerve (cranial nerve IX) on the posterior tongue.

The ability to perceive the taste and somatosensory sensations of foods and beverages varies normally with genetics. Genetic taste variation was discovered in the early half of this century (2). Some individuals (nontasters) are taste-blind to 6-n-propylthiouracil (PROP), whereas others find it bitter (tasters). Family studies (3) have shown that non-tasters carry two recessive alleles for the trait. More recently, Bartoshuk and colleagues (4,5) described two phenotypical subgroups among tasters: Supertasters taste the most intense bitterness from PROP and medium tasters less so. Supertasters may carry two dominant genes for the PROP trait (11) and perceive more intense taste sensations from many compounds (see reference 5 for a review). For example, supertasters perceive more than twice as much bitterness from black coffee as nontasters do (6). This could have implications for cancer therapies: Supertasters could experience more bitterness from chemotherapeutic medications than do nontasters, even if delivered intravenously (see the section Chemotherapy and Taste). Anatomical studies show that supertasters have the most fungiform papillae (and thus the most taste buds) (4,7). Because taste buds are innervated by fibers that carry touch and pain (8), super-tasters also perceive the most intense textural sensations from foods (e.g., creamy or viscous sensations from fat in foods) (7,9) and the greatest burn from oral irritants (e.g., black pepper, chili pepper, alcohol, carbonation). Greater pain innervation suggests that supertasters would also perceive greater pain from oral lesions. The gene for PROP tasting appears to reside on chromosome 5, with a related region on chromosome 7 (10).

Changes in sex hormone levels in females may influence sensory intensity or affective response to tastants and odorants.During childbearing years, variability in taste (12) and olfactory perception (13) are associated with menstruation and pregnancy. It may be that these senses, particularly taste, are upregulated during childbearing years to support a healthy pregnancy. For example, the perceived bitterness of quinine hydrochloride increases in the first trimester of pregnancy (14). Because poisons are often bitter, enhanced bitter perception could hinder maternal ingestion of substances harmful to fetal development. During menopause, taste— particularly bitterness (15), and possibly olfactory perception (16)—may be vulnerable to declines. Chemotherapeutic agents that alter sex hormone levels could change oral sensations by affecting taste and olfactory perception.

SOURCES AND POTENTIAL THERAPIES FOR ORAL SENSORY DISORDERS

Alterations in perception of food flavor through changes in taste, oral somatosensation, and retronasal olfaction can have a devastating effect on an individual. Living with chronic oral pain, a salty taste, or an inability to experience food flavor can obviously have tremendous impact on one's day-to-day life. Although these are extreme (but not uncommon) experiences, less severe dysfunction—such as heightened bitter intensity, diminished sweet perception, or faded flavors—can also reduce quality of life.

Taste Disorders

Taste is a remarkably robust sense; and ageusia, or total loss of taste, is rare (17). Interactions between the cranial nerves that mediate taste are responsible for some of this stability. This has been seen in clinical and experimental studies for interactions between cranial nerves VII and IX (18,19,20 and 21). Although the nerves responsible for taste sensation do not interact in the periphery, the areas to which they project within the brain appear to inhibit one another. For example, if one of the nerves is damaged, the inhibition produced by that nerve declines and taste responses from the other nerve are intensified. This intensification appears to compensate for taste lost from the damaged nerve (i.e., release of inhibition). Unilateral or bilateral insult to taste-related nerve(s) is detectable by applying tastants to the tongue and palate that correspond to cranial nerve innervation (18). For example, the chorda tympani branch of cranial nerve VII is vulnerable to viral (e.g., otitis media, influenza) and mechanical (e.g., head trauma, surgery) damage, leading to unilateral or bilateral losses of bitter taste on the anterior tongue (22). Taste may also be altered with medications (23). Some regional taste losses may not alter whole mouth taste perception (24) because the localization of taste sensations is controlled by the sense of touch (25). However, losses of chorda tympani taste may contribute to taste and oral sensory alterations.

One of the most disturbing taste alterations is dysgeusia, the presence of a chronic taste in the mouth (e.g., bitter, salty, metallic). In many cases, the dysgeusia results from an actual stimulus that has gained entry to the mouth (e.g., reflux, postnasal drip, infection, medications in saliva or gingival fluid). If a taste is not localized (i.e., it seems to come from all over in the mouth) and can be rinsed from the mouth even briefly, the taste may reflect an actual stimulus. Topical anesthesia of the mouth abolishes such sensations.

Dysgeusia can also reflect abnormal activity in a neural structure mediating taste. Taste sensations produced in this way are akin to phantom limb sensations and tinnitus; we call them *taste phantoms* (26). There is still much to be learned about taste phantoms, but what we have learned to date can provide some clues to their origin.

At least two types of taste phantoms can originate from the central nervous system. The first type results from direct stimulation of a neural structure. In one case, a prosthesis in the middle ear of a patient accidentally stretched the chorda tympani nerve, resulting in bitter and metallic taste sensations (27). Damage can also stimulate input. When a nerve is severed, the site of damage can produce a neural signal that is interpreted as taste sensation in the central nervous system. As recovery proceeds, a neuroma may form. Pressure on the neuroma can produce a continued neural signal. Phantoms of this type are usually intensified by topical anesthesia of the mouth. The topical anesthesia abolishes the taste input responsible for generating central inhibition; this releases inhibition on the phantom, making it intensify.

The second type of taste phantom results indirectly from the presence of inhibitory connections. Damage to one nerve releases inhibition of the other. This not only produces intensification of taste but also can produce taste sensations in the absence of any stimulus (i.e., taste phantoms). As yet, we do not know how such phantoms are produced centrally. One possibility is that spontaneous activity from uninjured sites becomes intensified enough by the release of inhibition to act as a stimulus. Such a possibility would explain why some release-of-inhibition phantoms are abolished when the area from which they seem to arise is topically anesthetized.

The uncertainties about the mechanisms of taste phantoms limit our ability to diagnose the source of every case of dysgeusia encountered in the clinic. However, we can conclude that if topical anesthesia of the mouth intensifies dysgeusia, it must originate in the nervous system (i.e., the dysgeusia can be classified as a taste phantom). Further, we should expect to find that dysgeusia in the presence of taste damage likely has neural origins as well. Dysgeusia produced in response to damaged nerves may diminish with regeneration of the nerves or mediation of the central processes that produce the phantom sensation. The average life of a taste receptor is 10 days but can extend to a month or more (28); thus, damaged taste buds are likely to regenerate, as are damaged neurons routing sensation to the brain. Phantom taste sensations (as well as phantom oral pain sensations) may respond to low doses of benzodiazepines, drugs that work on the central processing of taste (see description in the section Oral Pain).

Olfactory Disorders

Individuals can suffer from olfactory perception that is diminished (hyposmia), absent (anosmia), and distorted (parosmia), as well as olfactory sensations without an odor stimulus (phantosmia). Loss of olfaction can result from interference with conduction of odorants to receptors and damage to the neural structures mediating olfaction (29). Reports of hypersensitivity to odors do not appear to be associated with altered perception (30).

Much of the study of olfactory dysfunction involves how well odors are perceived through the nostrils (orthonasal olfaction). However, clinical evidence suggests that retronasal olfaction (perception of the odor component of food flavor through the mouth) may dissociate from orthonasal olfaction; this could have implications for oral sensation and sensory perception of foods and beverages.

Conductive damage includes all of those occasions in which the delivery of stimuli to the olfactory epithelium is impeded, whether through obstruction or swelling in the paranasal sinuses or interference with the mouth movements necessary to pump odors from mouth to nose. The olfactory nerve (cranial nerve I) can be damaged by viruses (especially from infection of the upper respiratory tract) as well as head trauma (31). Patients with upper respiratory infection-related olfactory loss (and head trauma) may exhibit parosmia (32). This occurrence may be similar to tinnitus and could potentially represent damage to the olfactory receptor cells (33). A less common but still prevalent cause of olfactory loss is repeated exposure to toxins (13). Degenerative diseases of the central nervous system (e.g., Alzheimer's or Parkinson's disease) (34) have olfactory dysfunction as a comorbidity. Olfactory perception also shows age-related declines (35). It is difficult, however, to distinguish olfactory losses associated with the aging process from those due to environmental insult.

Retronasal olfaction occurs naturally with eating and is tightly integrated with taste and touch sensations. Chewing and mouth movements warm and release olfactory volatiles from foods and beverages, and mouth and swallowing actions create sufficient intraoral pressure to pump volatiles to the olfactory receptors (36). Conditions that alter chewing, mouth, and swallowing movements can thus decrease retronasal perception, even if the olfactory system is intact (e.g., maxillary dentures) (37). Damage to touch sensations or chorda tympani taste may also impair retronasal olfaction. Historically, touch has been thought to help localize retronasal olfaction to

the mouth (38), but anecdotal and experimental evidence suggests that taste is necessary for full retronasal perception. Individuals with damage to taste, including those with damage after radiation therapy (39) or unilateral chorda tympani section during stapedectomy (24), report reduced retronasal olfactory sensations. Experimentally, unilateral anesthesia of the chorda tympani nerve reduces retronasal olfaction on the anesthetized side (40). It appears that both taste and touch sensations need to be intact to experience full retronasal olfaction. Retronasal olfaction and not orthonasal olfaction can be intact in subjects who have undergone a total laryngectomy (41,42). The laryngectomy interrupts the normal path of air traveling from the nose or mouth to the lungs and allows the individual to breathe through a stoma in the throat. Orthonasal olfaction is impaired because the air carrying odors does not pass through the nostrils during breathing; retronasal olfaction is intact because swallowing pumps the olfactory volatiles to the olfactory epithelium.

Olfactory neurons are capable of regeneration at all points between the receptor site and the central nervous system (43,44), although, as demonstrated with head trauma, the degree of regeneration may depend on the severity of damage (45), and perception may be blunted or distorted (46). Conductive losses may respond to therapies with topical steroids (47) or restoration of oral health to improve release and transport of odors from foods and beverages.

Oral Pain

Cancer and cancer therapies can cause oral pain, which impedes eating and the ability to obtain adequate nutrition. In this section, we discuss topical capsaicin as a potential treatment for the acute oral pain resulting from tissue damage. In addition, we discuss burning mouth syndrome, a chronic oral pain that appears to be central in origin (i.e., a phantom sensation). Cancer patients, because of the cancer or its therapies, may suffer from oral pain from lesions as well as from central sources.

Capsaicin, the active ingredient in chili peppers, produces a burning sensation when applied to the skin or mucous membranes, yet it desensitizes polymodal nociceptors if there is sufficient exposure, followed by removal of the capsaicin stimulus (48). Desensitization is particularly effective in the oral cavity (48,49) because capsaicin crosses the oral mucosa effectively (50). Capsaicin desensitization offers another benefit over topical anesthetics: Pain control can last much longer than results with topical anesthesia. In experimental studies with healthy subjects, complete recovery from capsaicin desensitization can take days (51). Capsaicin does not desensitize mechanoreceptors; thus, it does not produce the numbness that can make eating difficult.

The clinical utility of capsaicin as a topical analgesic depends on minimizing its burn and maximizing desensitization (52,53) as well as providing the analgesic in an acceptable form. Bone marrow transplant recipients, who have high risk of oral mucositis, report preferring nonviscous, room-temperature products with limited flavor (54). We have delivered capsaicin (via cayenne pepper) in a taffy candy (53); allowing patients to sample the candy to find the amount of cayenne pepper that provides a minimal burn before oral pain improves patient acceptance (55). Dietary use of capsaicin and taste genetics may influence the preferred level of capsaicin (supertasters, as already mentioned, experience more irritation from capsaicin) (56).

Patients can also apply capsaicin as diluted Tabasco sauce directly to lesions. Full strength Tabasco sauce is equivalent to 300 ppm capsaicin; this produces a very strong burn in someone who is not desensitized (individuals who use Tabasco sauce frequently report much lower burn). Diluting the Tabasco sauce 1:3 or 1:4 parts and applying this dilution to the lesion with a cotton-tipped swab for 30 seconds to 1 minute should produce sufficient exposure to desensitize the pain receptors and provide pain relief. The patient can try reapplication of the capsaicin as candy or directly to the lesion as needed. Subsequent applications may require less capsaicin to maintain the desensitization (57).

Oral pain in cancer patients, in some instances, may be similar to the oral pain of burning mouth syndrome (BMS). The severity of oral pain in BMS appears to be associated with genetic variation in taste and chorda tympani taste loss (58). Taste and oral pain (cranial nerve V) appears to show the same inhibitory interactions as seen between taste from cranial nerves VII and IX. Temporary anesthesia of the chorda tympani nerve can produce increases in the burn of capsaicin particular to genetic supertasters (59). Grushka and Bartoshuk (58) have suggested that BMS is an oral pain phantom in susceptible individuals. Genetic supertasters, defined by the density of fungiform papillae, report the most oral pain from BMS (60). Those who suffer from BMS show diminished or absent chorda tympani nerve taste (60). BMS also afflicts primarily postmenopausal women. The loss of bitterness associated with menopause (15) may act to release the inhibition on oral pain and increase the risk of BMS in susceptible individuals. There is some evidence that the oral pain of BMS may respond to benzodiazepines (58). The rationale for this treatment is that the oral pain is centrally mediated, and possibly controlled, through the trigeminal nucleus of the medulla. Taste appears to inhibit oral pain through gamma-aminobutyric acid (GABA). Clonazepam, a GABA receptor agonist, intensifies the inhibition produced by GABA, and thus can suppress the oral pain and taste phantoms. Low doses of clonazepam can diminish oral burn and dysgeusia in seven of ten patients treated (61,62). Cancer patients who suffer from oral pain that is not responsive to topical agents may benefit from drugs such as clonazepam, which act centrally.

PSYCHOPHYSICAL ISSUES IN THE STUDY OF TASTE AND CANCER

Anecdotal accounts from patients provide convincing evidence that eating can be a very unpleasant experience for many cancer patients. Gilda Radner describes her taste problems with chemotherapy in her book, *It's Always Something* (63):

> My taste buds were weird. Things tasted weird . . . eating was very unpleasant. I ate what I ordinarily wouldn't eat. I wanted cheeseburgers, cheese, and pickles. Lettuce and vegetables tasted like plastic. The highly salty, tasty things were good, but bland foods tasted like something they weren't and that was too strange. It was too weird when a carrot tasted like a ceramic kitchen magnet.

This provides a wonderful example of the difficulty in discerning the source of the alterations. For example, “lettuce and vegetables tasted like plastic” suggest an olfactory loss, yet Ms. Radner's ability to taste salt remained. “Eating was very unpleasant” could reflect a pure hedonic change or could reflect sensory abnormalities. If we are to provide relief to patients, we must document these changes with careful psychophysical testing. However, the psychophysical methods that can reveal real changes in the patient's chemosensory world are deceptive. They often look very simple but in reality require considerable skill both in execution and in interpretation. In the next sections of this chapter, we discuss the problems encountered in any psychophysical evaluation of abnormal sensory experience, review the cancer data with those problems in mind, and suggest appropriate study designs for future research. It should be noted that the best designs to determine whether an illness or therapy affects sensory experience is a prospective design in which each subject can be his or her own control. With such designs, patients can be tested before and after a given therapy. However, such designs are impractical when studying an illness. Therefore, the determination of whether cancer per se affects sensory experience is a much harder task than the determination of whether a particular therapy affects sensory experience. Obviously, in a clinical setting, an extensive psychophysical evaluation of each cancer patient is impractical. At the end of this chapter, we provide a brief list of suggestions that may help clinicians identify the source of food complaints.

THRESHOLD VERSUS SUPRATHRESHOLD EVALUATIONS

The threshold of a particular substance refers to the lowest concentration a subject can either detect or recognize. Threshold measurement seems a simple enough concept, but many experimental artifacts exist to plague accurate measurement, and some of the methods that have been used extensively in studies of taste and cancer are open to serious criticism. That aside, even when taste thresholds are measured with appropriate procedures (64,65 and 66), thresholds provide little information of value for cancer patients. Thresholds merely measure the bottom of the range and cannot demonstrate the actual effect of cancer or its therapies on a patient's taste world. The bottom of the range does not predict perceived intensities of foods and beverages because they are at higher concentrations (i.e., suprathreshold).

Figure 11-3 illustrates some dissociations between threshold and suprathreshold perception for sweet and bitter. We have selected these qualities because they are especially relevant to an explanation of the flaws in one of the most cited cancer papers (67). We discuss that paper in more detail later in this chapter. The two top panels show psychophysical functions for sucrose (i.e., perceived sweetness plotted against sucrose concentration). In both cases, the threshold (i.e., the approximate concentration at which sensation is zero) is elevated. The panel on the left shows taste loss associated with upper respiratory infection across the whole concentration range (68,69); this kind of change involves both a threshold shift and a reduction in perceived intensity. The right panel shows an elevated threshold (produced by adapting to sucrose), but no change in perceived intensity of the highest concentrations (65).

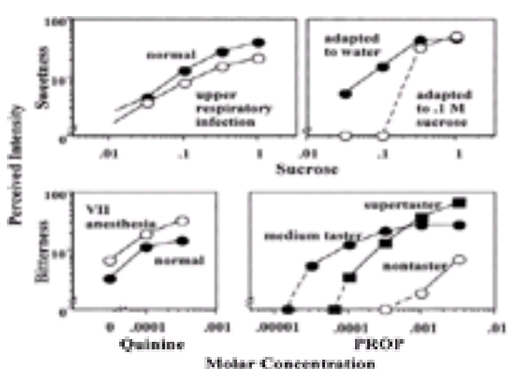

FIGURE 11-3. Psychophysical functions for sweet and bitter (see text for explanation). Upper left (68,69); upper right (65); lower left (20); lower right (22). PROP, 6-*n*-propylthiouracil.

The two bottom panels show psychophysical functions for the bitter compounds quinine and PROP. The panel on the left shows the results of a study in which quinine was swabbed onto a circumvallate papilla on one side of the tongue. The "normal" function shows the bitterness before anesthesia to the chorda tympani nerve on the contralateral side (20), and the "anesthesia" function shows the bitterness after anesthesia. Note that even water tasted bitter after the anesthesia, and that the bitterness of the quinine solutions was intensified. The panel on the right shows the thresholds and psychophysical functions for three individuals: a nontaster, a medium taster, and a supertaster of PROP. The thresholds for nontasters are clearly elevated above those for tasters (medium and super), and the suprathreshold intensities for nontasters are reduced below those of tasters; among tasters, thresholds do not completely predict how bitter PROP tastes at suprathreshold concentrations. Although individuals who taste PROP to be intensely bitter (i.e., supertasters) have lower PROP thresholds on average than those who taste PROP to be only moderately bitter (i.e., medium tasters), there are many reversals. The medium taster in the lower right panel actually has a lower threshold than the supertaster. These kinds of dissociations between threshold and suprathreshold intensity have been well documented in taste (65,70,71).

CANCER AND BITTER THRESHOLDS

DeWys and Walters (67) reported that cancer patients had high detection and recognition thresholds for the sweet taste of sucrose and that a subgroup of cancer patients had unusually low recognition thresholds for the bitter taste of urea. The authors stated, "The decreased taste symptom correlated with an elevated taste threshold for sweet (sucrose), and the symptom of meat aversion correlated with a lowered taste threshold for bitter (urea)." However, the conclusions are compromised by a miscalculated c^2 test (72). Correcting the statistical errors leads to the following corrected conclusions:

1. The sucrose detection and recognition thresholds were significantly elevated (although the c^2 reported for the recognition threshold, 59.4, should be 5.94).
2. The urea thresholds were *not* significantly lowered c^2 was reported to be 10.5, but the correct value is 1.05, which is not significant).
3. Patients with subjective taste loss did have significantly elevated sucrose recognition thresholds.
4. Patients with meat aversions did have significantly lowered urea recognition thresholds.

Gallagher and Tweedle (73) tested cancer patients before treatment and reported significantly lower urea thresholds, confirming the DeWys and Walters conclusion that we now know is incorrect. The data were not provided in the paper and, therefore, their Mannwhitney U tests cannot be checked. However, because means and standard errors were provided, we can calculate *t* tests. The *t* test for cancer patients versus controls was $t = 0.943$, which is clearly not significant. Thus, a second claim that cancer per se lowers urea thresholds does not appear to be correct.

Hall et al. (74) studied gastrointestinal (GI) cancer patients before treatment and reported (correctly) that a subgroup had urea thresholds lower than both noncancer GI patients and normal controls. However, GI noncancer patients had lower urea thresholds than the normal controls, casting doubt on any conclusions about cancer per se. Further, the patients with low urea thresholds did not have meat aversions. Other studies (75,76 and 77) found no differences between bitter thresholds in cancer patients who had not received chemotherapy or radiation therapy and control subjects. Bolze and colleagues (78) reported *elevated* thresholds for urea. In this study, cancer patients were significantly older than control subjects, and taste thresholds are known to rise with age. For this reason, we reanalyzed the data using only cancer patients and controls younger than 60 years of age. Urea thresholds were still elevated for cancer patients.

These studies do not support the conclusion that cancer lowers bitter recognition thresholds, rendering meat unpalatable because of its bitter components. However, even with the statistical errors, a few patients did have urea thresholds that were very low. These low thresholds raise additional issues regarding bitter thresholds that may be especially relevant to cancer patients. First, bitter dysgeusias have been reported by cancer patients, most often in connection with chemotherapy. The presence of a bitter dysgeusia could affect the measurement of bitter thresholds. For example, the Henkin threshold procedure (66,79) presents the patient with three drops, two of water and one containing the tastant. The concentration of tastant at which the subject consistently detects the correct drop is the detection threshold; the concentration at which the subject consistently selects the correct drop and provides the correct quality is the recognition threshold. Detection thresholds are generally lower than recognition thresholds. Weiffenbach (J. M. Weiffenbach, personal communication, 1998) has noted that if a patient has a chronic bitter taste in her or his mouth, the recognition threshold is the same as the detection threshold because all three drops taste bitter; thus, bitter thresholds appear reduced.

Another issue relevant to bitter taste and cancer is the suggestion that certain types of cancer are not randomly distributed among nontasters, medium tasters, and super-tasters of PROP. For example, Milunicová et al. (80) found fewer nontasters than expected among women with malignant tumors of the thyroid gland, breast, uterus, and ovary. If there is an association between type of cancer and type of PROP taster, it may be mediated through acceptance of bitter-tasting fruits and vegetables as well as bitter phytochemicals that are linked with cancer prevention (81). For example, PROP supertasters report less preference for cruciferous vegetables (81) and less frequent intake of green vegetables than do nontasters (82). If PROP tasting influences cancer risk through food preferences and intake, then we would expect to find variations in bitter taste thresholds across cancer patients.

Incidentally, food aversions are not explained by lowered bitter thresholds. Food aversions are far more likely to reflect bitter dysgeusia or conditioned aversions.

SELECTION OF APPROPRIATE CONTROLS FOR PATIENT-CONTROL DESIGNS

To match controls to patients, one must know all of the relevant variables affecting the illness. Any failure to do this renders the conclusions of the study suspect. Obviously, if we knew all of the relevant variables, the investigation at hand would probably be unnecessary; thus, we are virtually never certain that a patient-control study is adequate. However, at the very least, variables known to affect the measure under study must be controlled.

Taste and olfactory thresholds rise with age (83,84). As we noted with Bolze et al. (78), some taste thresholds were higher among cancer patients (tested before radiation therapy) than among controls; however, the patients were significantly older than the controls with which they were compared. A reanalysis of their data using only subjects younger than 60 years of age diminished the age difference, as well as the impact of some of the results. Bolze et al. measured detection and recognition thresholds for stimuli representing the four taste qualities (sweet, salty, sour, bitter); detection thresholds for sodium chloride (NaCl), hydrochloric acid (HCl), and urea (but not sucrose) were elevated, and recognition thresholds for HCl and urea were elevated. Our reanalysis showed significant elevations for the HCl recognition threshold and for both the urea detection and recognition thresholds.

The ability to taste varies genetically. To the best of our knowledge, no published paper on taste and cancer has attempted to control for this genetic variation. As we noted, some authors have suggested the possibility of connections between cancer and PROP tasting. Any such connections are especially important where patient-control studies claim lowered bitter thresholds.

Because the incidence of particular types of cancer is associated with risk factors (e.g., smoking, alcohol abuse), the impact of these risk factors on taste and smell must be considered in the selection of controls. In addition, effects of cancer on incidence of diseases like upper respiratory infections may also produce non–cancer-related differences between patients and controls.

LIMITATIONS ON THE SUPRATHRESHOLD TECHNIQUES USED TO COMPARE PATIENTS VERSUS CONTROLS

Suprathreshold scaling reflects the oral sensory world that is most relevant to everyday experiences such as eating and drinking. Suprathreshold scaling produces psychophysical functions that allow us to see how perceived intensity changes across the entire range of sensation from barely detectable (near-threshold) to the most intense sensations possible. This is the most important information but also the most difficult to obtain because we cannot share another person's experiences directly. We have reviewed this dilemma in the context of studies on aging (83) and genetic variation in taste (5,85); we briefly summarize that argument in the next section.

COMPARING SENSORY EXPERIENCES

How do we compare sensory experiences? We do so by finding a standard to which other sensations can be compared. One of the oldest methods is to use the adjectives on labeled selfrating scales (Likert, category, visual analog) as standards. For example, with the Natick 9-point category scale we tell subjects to apply numbers to their sensations, such that 1 = "very weak," 5 = "medium," and 9 = "very strong." These scales were originally used for measuring changes or differences within a person and are valid for such usage. But to make comparisons across subjects, we must assume that everyone applies these adjectives to their perceptions of intensity in the same way, so that if two people both call a stimulus very strong, they are perceiving the same absolute intensities. This is an incorrect assumption unless the adjectives are applied to a specific domain. This point was made by S. S. Stevens over 40 years ago: "Mice may be called large or small, and so may

elephants, and it is quite understandable when someone says it was a large mouse that ran up the trunk of the small elephant." If cancer patients and controls have different oral sensory worlds, the absolute intensities of the adjectives will be different; members of the group will stretch or compress the labeled scales to apply to the context of their oral sensation. This could minimize, reverse, or fail to detect the true oral sensory differences between cancer patients and controls.

Another way to find a standard is to use another sensory experience. For example, when we explore genetic variation in taste, we use the intensity of a sound as a standard. We essentially ask subjects to match the intensity of a taste to the intensity of a sound. We know that hearing varies, but we have no reason to believe that variations in hearing and taste are related. Thus, on average, we discover that supertasters match saturated PROP to a very loud sound, whereas nontasters match the same concentration to a very soft sound. The use of one sensory modality as a standard for variation in another is called *magnitude matching* (86). This method is usually used with the psychophysical method called *magnitude estimation* but is applicable to any suprathreshold scaling technique.

Research on oral sensory differences between PROP non-tasters and supertasters may provide insights on how to measure oral sensory differences between cancer patients or cancer patients and controls. Green and colleagues (87,88) empirically derived an adjective-labeled scale that has ratio properties. The labeled magnitude scale (LMS) has adjectives spaced such that distances along this scale are approximately logarithmic and essentially equivalent to magnitude estimates (i.e., if two stimuli produce responses of 8 and 4, respectively, the first stimulus is perceived to be twice as intense as the second). To avoid the relative meaning of the adjective on the scale, we propose that the top of the LMS be labeled as "strongest imaginable sensation of any kind" (85). This scale would therefore not be confined to a specific sensory modality but rather have meaning across all domains (Fig. 11-4). Preliminary findings reveal that use of the general LMS detects oral sensory differences among PROP taster groups and associations with dietary behaviors that have not previously been seen.

FIGURE 11-4. The general labeled magnitude scale (85,87,88) may provide a universal sensory ruler to obtain ratings of perceived sensory experience that are comparable across individuals (see the section in the text, Comparing Sensory Experiences). The scale contains descriptors that are used in everyday life, ranging from nothing at the very bottom to strongest imaginable sensation of any kind at the top. To obtain ratings of intensity, patients should read the descriptors of intensity, be instructed that the top of the scale is across any sensory domain, including experiences that may be painful, and indicate their rating of intensity at any location on the line.

Another psychophysical error is to give a standard to both patients and controls and tell them what rating the standard represents. This forces patients and controls to give the same ratings even if they are having very different experiences. The results, which will show no difference between patients and controls for the standard, are meaningless. This mistake is easy to make because the practice of providing a standard and assigning it a rating is common when individual differences are not important. Consider the following example: Ames et al. (89) studied the taste of NaCl and sucrose in patients with breast cancer using a method designed for studies related to food (90). The subjects were presented with a 15-cm horizontal line with the end points labeled "least salty/sweet" on the left and "most salty/sweet" on the right. Subjects were given the most extreme taste concentrations (e.g., 0.040 and 0.756 M NaCl and sucrose) and told that these corresponded to the labels. Subjects were then instructed to mark the line to indicate the perceived intensity of each sample. Note that if the cancer patients had perceived all tastants as weaker than the controls did, this would never have been revealed because cancer patients and controls alike were instructed to rate the top concentration at the most salty/sweet end of the scale. Not surprisingly, there were no differences between cancer patients and controls.

DISTINGUISHING HEDONIC FROM SENSORY ALTERATIONS

Taste and smell not only provide sensory information but also affect pleasure and displeasure. The hedonic attributes of taste and smell serve different functions. The affect of taste is hard-wired; newborns respond to sweet tastes with facial expressions suggesting pleasure, and to bitter tastes with facial expressions suggesting displeasure (91). On the other hand, the affect of olfaction appears to be largely (if not completely) learned. At 2 years of age, children do not appear to experience adult-like pleasure and displeasure from odors (92,93); by 3 years, their responses begin to resemble those of adults (94).

The affect of taste is relatively stable, but the affect of olfaction is quite labile. Simple exposure to an odorant can change its pleasantness (95). Pairing an odor with pleasurable experiences like sweet taste (96) or calories (97) can increase its pleasantness, and pairing an odor with nausea decreases its pleasantness (98). This latter phenomenon plays an important role in the formation of conditioned food aversions.

When patients say that food does not taste good, they may be referring to a genuine sensory alteration or to a hedonic change: Food tastes just as it always did, but that taste is no longer pleasant. It is important to question patients to be sure that the nature of the complaint is clear.

ORAL SENSORY ALTERATIONS ASSOCIATED WITH CANCER AND ITS RELATED THERAPIES

Most of the literature on oral sensory alterations is focused on taste. For that reason, the discussions in the next sections are also focused on taste. What is known about genuine cancer-related sensory alterations in olfaction is summarized later. Conditioned aversions, which reflect hedonic rather than sensory alterations, involve olfaction; these are discussed toward the end of this chapter.

REAL-WORLD TASTE EXPERIENCE AND CANCER

Tumors can obstruct chemoreceptor sites, interfere with neural transmission on the pathway between receptor site and the brain, and affect sensory processing in the brain itself. Several types of intracranial tumors are known to alter both taste and smell. Acoustic neuromas (also called *vestibular schwannomas*), which form on cranial nerve VIII, can produce taste loss if the tumor invades cranial nerves VII or IX (18).

There are two sources of evidence for meaningful taste loss in cancer patients, suprathreshold psychophysical studies and anecdotal reports. We have already discussed the study by Ames et al. (89) on breast cancer patients. Because these patients had only surgery (no chemotherapy or radiation therapy), they would have been appropriate to study. However, the results—that there were no effects of cancer per se—were produced by the misuse of the scaling method and have no relevance to cancer per se.

Mossman and Henkin (99) used a different suprathresh-old scaling method that can reveal differences between cancer patients and controls. The method used, forced scaling, asks subjects to rate the intensity of taste on a scale from 1 to 100, in which 100 equals the most intensely salty, sweet, sour, or bitter solution ever experienced. Patients with head and neck cancer rated taste intensities lower than control subjects did. Only one of the patients, however, was subjectively aware of any taste loss, which is hard to reconcile with the psychophysical data. This kind of method has a potential flaw for examining differences across groups. The subjects were asked to rate their sensations in comparison to their most intense taste experience. However, the most intense taste experience varies with genetic variation in taste. This means that differences between patients and controls may simply reflect genetic differences. Fortunately, this study also includes within-patient comparisons, which are discussed in the section on radiation therapy.

Anecdotal descriptions may offer insight into the status of taste function in cancer patients, but the anecdotes must contain sufficient information to ensure that the patient is reporting true taste changes. Bolze et al. (78) reported that 17% of their patients had subjective complaints of loss of taste or abnormal taste when initially interviewed, but did not describe how their questions were phrased. Kashima and Kalinowski (100) argue that taste function is frequently disturbed before treatment of laryngeal cancer. However, the phrasing of their questions is not included in their report, and they were dealing with patients who may also have experienced oral sensory alterations from some of the risk factors for this cancer (e.g., tobacco and alcohol use). Some reviews of cancer and taste assert that cancer damages taste (101), but the evidence turns out to be the untrustworthy threshold studies already discussed. Finally, some reports of alterations in taste perception are actually

assessments of changes in the palatability of foods (102). In conclusion, there is no good evidence for a general phenomenon of taste loss with cancer per se.

CHEMOTHERAPY AND TASTE

Cancer therapies often suppress tumor growth by interrupting the proliferative capacity of cancer cells and can have both a direct and indirect impact on taste, smell, and oral somatosensation. Tissues in the oral cavity are particularly susceptible to damage because they divide at a faster rate than tissues of other organs. Both chemotherapy and radiation therapy can damage chemosensory structures, disrupt saliva (103) and mucus production, and cause oral mucositis, xerostomia, and dental caries. Antiestrogen drugs, such as tamoxifen citrate, can alter the body's hormone production, which might diminish bitterness (12); chemotherapy drugs can also enter the mouth via gingival fluid (104) and saliva (105,106) and stimulate taste, tactile (107,108 and 109), and olfactory (110) sensations. The existence of venous taste was once exploited in the calculation of circulation time; compounds were injected into the blood-stream, and the length of time that passed before they were tasted in the mouth was used as a measure of circulation (111,112). These compounds stimulate taste receptors on the lower portions of the taste cells directly from blood without actually entering the mouth.

The effect of chemotherapy on a patient's experience with food can often be dramatic. One study demonstrated that over 80% of chemotherapy patients avoided food (113). Many reported taste alterations, as well as dry mouth, have been directly linked to drugs such as vinblastine sulfate, cisplatin, bleomycin sulfate, doxorubicin, or methotrexate (28,114). The worse the perceived taste alterations, the worse the reported distress and change in quality of life (114). A study by Soni and Chatterji (115) using electrogustometry (i.e., assessment of thresholds for electric taste) reported that 10% of the patients treated with bleomycin sulfate showed elevated thresholds (compared to control subjects), but that thresholds returned to normal within 10–12 weeks. This paper illustrates a point already made: Localized loss often fails to affect realworld perception. Electrogustometry uses a metal probe to stimulate the tongue. The probes are very small and so the stimulation is very localized. Soni and Chatterji reported that only one of five subjects who showed substantially elevated thresholds noticed any loss.

Two suprathreshold psychophysical studies have failed to find significant effects of chemotherapy. Trant et al. (116) used a 10-cm line labeled “no sweetness, sourness, saltiness, or bitterness” on the left and “extremely sweet, sour, salty, or bitter” on the right (subjects were allowed to extend the line if they chose). The intensity scores were not reduced in those patients receiving chemotherapy (compared to other cancer patients), but psychophysical limitations could have failed to detect differences. Mulder et al. (117) asked patients to rate taste intensities on a 7-point scale labeled with 0 = “no taste” and 7 = “extremely strong.” Patients were tested before chemotherapy and between the seventh and tenth days after the last day of nine courses of chemotherapy. Following chemotherapy, the lowest concentrations were rated stronger than before and the highest concentrations were rated lower than before, the most pronounced effect being on sweet. Note that this is a relatively subtle loss, yet Mulder et al. quote one of their patients as saying, “Everything tastes the same.”

The discrepancies between the results of these studies and patient anecdotes suggest several problems. Experimental designs may fail to capture the important effects of chemotherapy on taste. Prospective studies following individual patients may be necessary to identify the critical time at which taste loss occurs, as well as to identify the tumor sites and chemotherapeutic agents most likely to produce damage. New psychophysical methods for suprathreshold scaling are more sensitive than the methods previously in use (5,85). Finally, patient anecdotes, such as “everything tastes the same,” actually suggest olfactory losses, and the effects of chemotherapy on olfaction have been virtually ignored.

RADIATION THERAPY AND ORAL SENSATIONS

The anecdotal accounts of radiotherapy-induced disturbances are compelling. MacCarthy-Leventhal, a physician who underwent radiation for cancer of the pharynx in the 1950s (39), described both a “blindness of the mouth,” rendering food tasteless, and a “hallucinatory” taste, over-whelming all liquids. These descriptors suggest alterations of taste, retronasal olfaction, and possibly oral somatosensation. More recently, Chencharick and Mossman (118) reported perceived changes in food taste and use of sugar in head and neck cancer patients. Before radiation therapy, 25% of these patients reported “changes in taste” and that “foods taste bad,” whereas 80% reported such changes after treatment. More than half of these patients noticed an abnormal taste with high-protein foods (e.g., meat, eggs, dairy) and a quarter reported adding sugar to foods. Protein molecules are too large to stimulate taste or smell receptors directly. It is possible that dysgeusia is more apparent when eating high-protein foods. These foods require chewing that could release bitter-tasting compounds (from oral health problems or medications) into the mouth through the saliva. Centrally mediated phantoms may also be more noticeable when ingesting high-protein foods. Bonanni and Perazzi [(119) cited in Rubin and Casarett (120)] followed 50 patients for 1 month to 1 year and reported both suppressed and heightened taste sensations. This is particularly interesting because there are theoretical reasons to expect radiation therapy to be associated with heightened taste. Because radiation is directed to specific areas, one might expect some taste nerves to be affected more than others. Localized damage can lead to intensified taste sensations due to release of inhibition. It is also possible that high-protein foods “taste” bad because of impaired retronasal olfaction with altered taste and oral touch sensations due to radiation therapy.

The taste losses induced by radiation are not subtle. Taste loss can occur within 2–3 days after the therapy, before the observed degeneration of taste buds at approximately 7 days posttherapy (121). The number of taste buds degenerated is related to the size of radiation therapy. Radiation therapy may cause dissociation between thresholds and suprathreshold taste, as demonstrated in a 52-year-old woman undergoing radiation therapy for a tumor of the neck (65). This patient's taste recognition thresholds initially rose but returned to normal after approximately 60 days. Her suprathreshold functions flattened and did not recover. She lived in a pastel taste world despite normal thresholds. A study by Mossman and Henkin (99) made within-patient comparisons of taste function before, 2 weeks after, and 5 weeks after radiation therapy. The psychophysical functions for taste flattened steadily during this time. In a study of the longterm effects of radiotherapy (103), taste losses were still present up to 7 years after therapy. However, taste loss with radiation therapy is by no means universal. Schwartz et al. (122) found only mild impairment in patients tested at varying intervals after therapy (6 months to 19 years).

CANCER, CANCER THERAPIES, AND OLFACTION

The effects of cancer per se and chemotherapy on the sense of smell have received very little attention. This may reflect the common misunderstanding about the proper distinctions between taste and smell. Anecdotal accounts suggesting that food is flat with no taste actually imply olfactory loss as well as genuine taste loss, because a large part of the sensory input from food is olfactory (perceived retronasally). Cancer therapies that alter taste and oral touch could also impair retronasal olfaction, even if they do not alter functioning of the olfactory nerve (cranial nerve I). The effects of radiation therapy on olfaction have been documented by Doty and his colleagues (123,124) and Ophir et al. (125). In the study by Ophir et al., patients did not show complete recovery even 6 months after treatment. The influence of cancer and related therapies on olfaction deserves more attention.

CONDITIONED FOOD AVERSIONS

Garb and Stunkard (126) provided a classic picture of a conditioned aversion: If a person becomes sick after eating a specific food, he may develop an intense dislike (i.e., *aversion*) for that food, regardless of whether it was responsible for the illness. Conditioned aversions were used in the treatment of alcoholism as early as 1940 (127). Subsequently, conditioned aversions became of great interest to learning theorists (128,129). Conditioned aversions to foods form in the presence of nausea (98) and can occur even when an individual recognizes that the nausea was not caused by the food. Nausea is associated with both chemotherapy and radiation therapy, but may also be associated with the cancer itself. Bernstein (130) was the first to show that conditioned aversions could be produced by therapies for cancer and to suggest that these aversions might play a role in the loss of appetite in cancer patients.

The roles that taste and olfaction play in conditioned aversions are scientifically very interesting. In animals, conditioned aversions are believed to form better to taste than to olfactory stimuli. In humans, conditioned aversions are rarely (if ever) specific to sweet, salty, bitter, and sour, but form instead to the odors of the food perceived retronasally (131). Part of this apparent difference between the results in animal and human studies may relate to confusion over the proper distinctions between orthonasal olfaction, retronasal olfaction, and taste. Rozin (132) has suggested that the brain may treat olfactory input differently depending on whether its origin is orthonasal or retronasal, because orthonasal input provides information about the environment, whereas retronasal input provides information about what is in the mouth. To the best of our knowledge, the olfactory stimulation in animal studies is orthonasal. If these studies had used retronasal olfactory stimulation, we would expect that the conditioning would be greater to retronasal olfactory stimuli than to taste stimuli.

Broberg and Bernstein (133) used the properties of conditioned food aversions to provide a behavioral intervention that helps prevent aversions to important dietary items in cancer patients. Children were given either root beer or coconut Lifesavers candy before chemotherapy. The Lifesavers candy served as a scapegoat food. Aversions were formed to the scapegoat, preventing formation of aversions to other foods. Andresen et al. (134) compared novel and familiar scapegoats and found that the novel scapegoat was more effective. Mattes (135) demonstrated the efficacy of this procedure in a large population that included patients receiving radiation therapy (not tested in the previous studies).

One of the interesting features of conditioned food aversions is that some foods become aversive and others do not. Bartoshuk and Wolfe (L. M. Bartoshuk and J. M. Wolfe, unpublished data) demonstrated this with aversions formed in college students as the result of illness induced by consumption of alcoholic beverages. Of 61 alcohol-induced aversions, about half occurred when the subject consumed more than alcohol alone (e.g., vodka and orange juice, beer and buffalo wings). In these cases, about 40% of the time the aversion skipped the alcohol altogether and formed to the accompanying food or beverage. The rest of the time the aversion included the alcoholic beverage. Jacobsen et al. (136) studied the development of aversions to diet items over successive chemotherapy sessions in cancer patients. They

found that 46% of the patients developed aversions to at least one food at some time during treatment. They concluded that the number of aversions formed was probably limited by the familiarity of the foods (animal studies indicate that novel foods condition more easily). In addition, consumption of several foods may have protected individual items.

Although it is clear that nausea produces conditioned aversions (98,137,138), some aversions appear to form in cancer patients that cannot be closely associated with nausea (135,136,139,140).

PHANTOM SENSATIONS RESULTING FROM CHEMOTHERAPY OR RADIATION THERAPY

Some patients report bitter taste sensations during chemotherapy (107,108 and 109). Because medications tend to taste bitter, patients may be tasting their chemotherapeutic drugs. There are two routes by which these drugs might stimulate taste. First, the drugs may gain access to the mouth via saliva (105,106) or gingival fluid (104). Second, the drugs may be perceived directly from the blood-stream through venous taste (141,142) or olfactory (110) sensations.

Cancer therapies can produce salivary disorders (e.g., dry mouth) that abet tissue damage; insufficient saliva leaves tissues unprotected and open to infection, the products of which can be both tasted and smelled.

Nesse et al. (143) reported pseudohallucinations associated with chemotherapy. Some patients described a chemical odor that occurred when they thought about or viewed the clinic. Two patients described being able to taste their chemotherapeutic drugs while under treatment, and then tasting them again when thinking about them. Olfactory hallucinations can occur in normal individuals who have been exposed to intensely emotional experiences. Burstein (144) reported two such hallucinations related to posttraumatic stress disorder. A woman who had been in an automobile accident smelled gasoline while riding as a passenger in her husband's car, and a man who had been in a fire reported flashbacks in which he smelled smoke as he had in the fire.

RECOMMENDATIONS

Even without extensive psychophysical testing, clinicians can distinguish sensory from hedonic complaints and can obtain information about the source of dysfunctions. Table 11-1 summarizes steps to evaluate sources of oral sensory complaints. Identifying the complaint's source can provide insights into potential therapies. Strategies designed to improve dietary intake and nutritional status should be individualized, as illnesses and treatments affect patients differently, making the application of universal recommendations to improve the flavor of food unwise. Patients are likely to benefit from consultation with a registered dietitian. Strategies designed to prevent chemosensory dysfunction secondary to treatment (e.g., minimizing damage to taste and olfactory receptors with shielding during radiation therapy) should be adapted to the needs of the patient (28). The National Cancer Institute has published a booklet, *Eating Hints for Cancer Patients*, which provides useful recipes for cancer patients and their families. Finally, it is important to reduce the impact of conditioned aversions.Studies suggest that

TABLE 11-1. EVALUATING ORAL SENSORY COMPLAINTS

- Patients should be informed of the possibility of a food aversion occurring with treatment.
- Patients should avoid eating 4 hours before and after chemotherapy or bowel irradiation (28).
- Patients may ingest a novel-tasting but nutritionally unimportant food (scapegoat) shortly before irradiation or chemotherapy (133).
- If possible, patients should not consume nutritionally important foods until nausea ends (134).

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12

DYSPHAGIA

STEVEN B. LEDER

The term *dysphagia* is derived from the Greek *dys* (with difficulty) and *phagia* (to eat). Passage of a food bolus from the oral cavity through the pharynx without penetration into the trachea constitutes a successful swallow. Dysphagia can occur due to disordered oropharyngeal swallowing or bolus penetration of the vocal folds and aspiration into the trachea and lungs.

When material penetrates the larynx and enters the airway below the level of the true vocal folds, aspiration has occurred. Aspiration can occur *before* the swallow (e.g., before triggering of the swallow reflex), *during* the swallow (e.g., due to poor laryngeal closure), or *after* the swallow (e.g., from residual material left supraglottically) (1).

Dysphagia results in higher health care costs due to increased length of hospitalization and the more expensive nature of nonoral feeding (2). Just as important, dysphagia impacts negatively on both eating and the activities associated with eating by restricting or preventing the normal act of swallowing (3,4,5,6,7 and 8).

Eating and life are bound together. Not only is eating one of life's greatest pleasures, but it is also necessary to sustain life itself. We eat for many reasons, including sustenance, satiety, and to satisfy hedonistic desires (3,4). Just as importantly, eating is integral to the social network of every society in the world (3,9). Annual feasts, seasonal celebrations, weekly meal planning, and daily treats help to define, order, and enrich a society's, a family's, and an individual's life (9,10,11,12,13 and 14). When an attendee at life's celebration cannot participate, the impact is immediate and significant (3,10). Inability to eat not only threatens biological survival but also represents a barrier to fully sharing life with one's family and society (4).

The impact of dysphagia on an individual's social, emotional, and psychological life and well-being has seldom been addressed in professional literature (15). A spousal report (16) discussed the importance of eating, for both the individual and his family, throughout the progression of neurological disease. When eating became impossible for patients, the family felt that even the smell of favorite foods brought pleasure and a sense of social connection and sharing between the patient and the family.

Only one scientific paper has dealt with eating and quality of life (4). It included an extensive discussion of the experiential meaning of eating, a theoretical framework that described dysphagia handicap and adaptiveness, outlined a model for understanding the dysphagic person's concealment of the disorder in the medical encounter, and proposed a strategy for professionals treating the disorder. Dysphagia intervention is intended to increase the patient's feelings of hope, security, and self-respect by focusing on adapting eating to the individual's psychosocial abilities and supporting the individual's feelings of hope for a meaningful life (4,17,18 and 19).

The adverse effects of both cancer and its treatment on swallowing are well known (20). Pretreatment dysphagia is caused by the tumor due to mass or neurological changes, which can lead to malnutrition and, at times, aspiration. Posttreatment dysphagia is caused by the treatment options, with surgery disrupting swallowing ability most significantly, but radiation therapy and chemotherapy, either alone or in conjunction with surgery, also contributing to the severity of dysphagia (20).

The purpose of this chapter is not only to discuss the anatomy and physiology of normal swallowing, etiologies of dysphagia, and diagnostic procedures, but to explore the importance of appropriate rehabilitation and psychosocial intervention with the patient and caregivers to foster an optimal supportive environment to either continue or reinstate the act of eating, with all its attendant social importance, into the daily life of the individual.

ANATOMY AND PHYSIOLOGY

Swallowing is a highly complex, sequential behavior with a number of interrelated and interdependent motor activity patterns that occur simultaneously and rapidly in a predetermined order. Successful swallowing is a function critical to a patient's emotional and psychosocial interactions (21), and it impacts directly on medical status due to the potential for aspiration pneumonia and other pulmonary complications (22,23 and 24).

It is not the purpose of this chapter to provide an extensive discussion of normal swallowing anatomy and physiology. A number of excellent sources are provided for a comprehensive discussion of this area [Miller (25,26), Logemann (1,27), Kennedy and Kent (28), Larson (29), Dodds (30), and Gelfand and Richter (31)]. However, a working understanding of normal swallowing anatomy and physiology is required before discussing the areas of disordered swallowing and dysphagia diagnostics and rehabilitation.

Figure 12-1 shows the anatomical structures involved in swallowing. Table 12-1 outlines basic swallowing response. The swallowing mechanism includes bony and cartilaginous support structures, striated and smooth muscle, and neural substrates. The act of swallowing shapes and moves a bolus from the oral cavity to the stomach by an ordered chain of events, commonly divided into the following four phases: oral preparatory phase, oral phase, pharyngeal phase, and esophageal phase. Dysphagia can occur during one or more of the four phases of swallowing.

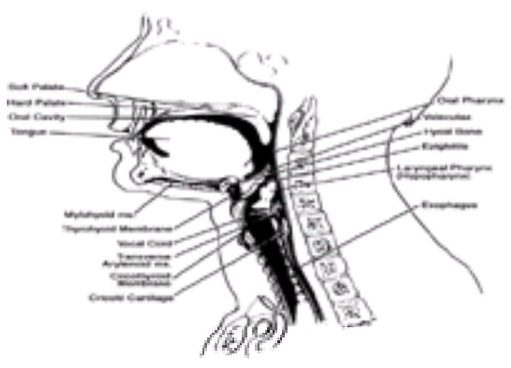


FIGURE 12-1. Sagittal view of the head and neck showing relevant musculoskeletal structures involved in swallowing. (From Kahrilas PJ. The anatomy and physiology of dysphagia. In: Gelfand DW, Richter JE, eds. *Dysphagia diagnosis and treatment*. New York: Igaku-Shoin Medical Publishers, 1989;11, with permission.).

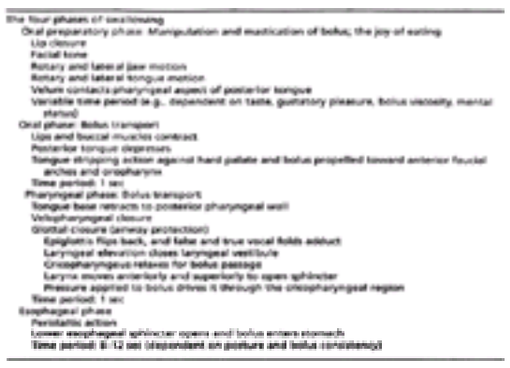

The four phases of swallowing
Oral preparatory phase: Mastication and mastication of bolus; the joy of eating
Lip closure
Facial tone
Rotary and lateral jaw motion
Rotary and lateral tongue motion
Velum contacts pharyngeal aspect of posterior tongue
Variable time period (e.g., dependent on taste, gustatory pleasure, bolus viscosity, mental state)
Oral phase: Bolus transport
Lips and buccal muscles contract
Posterior tongue depresses
Tongue stripping action against hard palate and bolus propelled toward anterior faucial arches and oropharynx
Time period: 1 sec
Pharyngeal phase: Bolus transport
Tongue base retracts to posterior pharyngeal wall
Velopharyngeal closure
Glottal closure (airway protection)
Epiglottis flips back, and false and true vocal folds adduct
Laryngeal elevation closes laryngeal vestibule
Cricopharyngeus relaxes for bolus passage
Larynx moves anteriorly and superiorly to open sphincter
Pressure applied to bolus drives it through the cricopharyngeal region
Time period: 1 sec
Esophageal phase
Peristaltic action
Lower esophageal sphincter opens and bolus enters stomach
Time period: 8–12 sec (dependent on posture and bolus consistency)

TABLE 12-1. BASIC SWALLOWING ANATOMY AND PHYSIOLOGY

Table 12-2 outlines the sensory and motor nerves (and their innervations) that are involved in swallowing. The neural control of swallowing involves four main components: efferent motor fibers of the cranial nerves and ansa cervicalis; afferent sensory fibers of the cranial nerves; cerebral and midbrain fibers that synapse with the brainstem swallowing centers; and the paired swallowing centers in the brainstem (30). The cranial and motor nerves and higher cerebral centers send input to the brainstem swallowing centers. The information is processed and, if the afferent neural input is appropriate, a swallow response is activated. The cranial nerves then carry the output signals to the muscles involved in swallowing.

Sense	Sensory area innervated	Cranial nerve	Motor area innervated
Touch	Soft palate, mouth, anterior ⅔ tongue, nasopharynx	V	–
		VII	Mastication muscles
		VII, VIII, C1–C2	Hyoid muscles
Taste	Anterior ⅔ tongue	VII	Facial muscles
Touch/taste	Posterior ⅓ tongue	IX	Stylopharyngeus, superior constrictor
Touch	Oro-hypopharynx	–	–
Touch	Tongue base, interior larynx	X	Palate,[a] pharynx,[b] larynx, esophagus
		XI	With X to larynx, pharynx, pharyngeal constrictors
Muscle[c]		XII	Intrinsic and extrinsic tongue muscles[c]
		C1–C2	Extrinsic tongue muscles[c]

[a]Except for tensor veli palatini innervated by V3.
[b]Except for stylopharyngeus innervated by IX.
[c]Except for glossopalatinus innervated by X.

TABLE 12-2. BASIC SENSORY AND MOTOR NERVES INVOLVED IN SWALLOWING

The exact nature of the neural circuitry that controls the oral, pharyngeal, and esophageal phases of swallowing is not fully known. Two theories, with the goal of explaining the neurological control mechanisms of swallowing, have been reported: the reflex chain hypothesis and the central pattern generator hypothesis (25). In the reflex chain hypothesis, a bolus moving in an anterior-to-posterior direction in the oral cavity and pharynx stimulates sensory receptors that sequentially trigger the next phase of swallowing. Swallowing occurs as a result of a chain of reflexes stimulated by and dependent on the previous response (i.e., the late oral phase starts the early pharyngeal phase of swallowing). In the central pattern generator hypothesis, sensory feedback does not influence swallowing behavior once a swallow has been started. The swallowing sequence is preprogrammed by the neurons in the medullary swallowing centers. Most likely, both theories play a role in the act of swallowing in that swallowing depends on a central pattern generator that is modified by, but not dependent on, feedback from sensory input (30).

ETIOLOGIES OF DYSPHAGIA

Head and Neck Cancer Surgery and Reconstruction

The act of swallowing, intermixed with respiration and speaking, is the most sophisticated coordination of voluntary and involuntary muscle action that exists in the animal kingdom (32). Dysphagia is a very common symptom in patients with head and neck cancer (33). Dysphagia is due to incoordination of the swallowing mechanism, obstruction, neurological changes, or pain caused by the tumor, and the combination of treatment modalities used [e.g., surgery for the resection of the cancer, external beam radiation therapy (EBRT), and chemotherapy]. Surgical resection of the oral, pharyngeal, laryngeal, or esophageal areas commonly results in varying degrees of dysphagia (1,32,34,35,36 and 37). The limiting factors relative to the type and severity of dysphagia are the number and amount of anatomical structures removed and the reconstructive procedure(s) used after the resection. In addition, patient motivation and the amount of individualized dysphagia rehabilitation impact on the rate of swallowing recovery (38).

The goal in the treatment of early tumors (stages I–II) is cure with surgical resection, EBRT, or both. Dysphagia rehabilitation is often not required in these patients, but when it is, the success rate for returning to a normal diet is excellent. The goal in the treatment of advanced tumors (stages III–IV) is locoregional control. This is accomplished by either organ preservation therapy [i.e., EBRT and chemotherapy (39,40,41,42,43 and 44)], with surgical salvage if necessary, or primary surgery followed by surgical reconstruction to allow for as much preservation of eating and speaking as possible. Organ preservation treatment may cause dysphagia due to mucositis, xerostomia, localized swelling, taste changes, and nausea. Surgical resection, however, often results in dysphagia, which may make eating very difficult (34). The patient's quality of life, dignity, and interpersonal relationships may become severely compromised, resulting in a reclusive behavior pattern and withdrawal from society (32).

Pretreatment Swallowing Function

To investigate outcomes of cancer treatment on swallowing, pretreatment baseline data on swallowing function are needed. Although early symptoms of head and neck cancer vary depending on site of lesion, dysphagia is often mentioned as a symptom of oral, pharyngeal, and laryngeal cancer. Little objective data, however, are available characterizing the swallow function in patients with head and neck cancer before treatment.

A multicenter database is currently evaluating the functional outcomes of swallowing in patients receiving speech pathology intervention after head and neck cancer treatment (45). This preliminary report outlines the rationale for the database and explores the complexities involved in obtaining reliable, long-term, accurate data collection in the head and neck cancer population. The goal is to obtain measures and predictors of “good functional outcomes” from mapping prospectively the path of rehabilitation of head and neck cancer patients.

Pauloski et al. (46) documented pretreatment swallowing function in 352 patients with various stages of oral, pharyngeal, and laryngeal cancer compared with a control group of age- and gender-matched subjects with normal swallow, and investigated the rate of patients' complaints of dysphagia before treatment. Head and neck cancer patients had significantly longer oral and pharyngeal transit times, greater amounts of oral and pharyngeal residue, shorter cricopharyngeal opening durations, and lower swallow efficiencies than controls. Swallow function worsened with increased tumor stage, and patients with oral and pharyngeal lesions had worse swallow function than patients with laryngeal lesions. However, despite these differences, the study population exhibited only a 4% aspiration rate, and in general, their swallows were efficient and highly functional before treatment. This is further reflected in the fact that 59% of patients had no complaint of difficulty swallowing before treatment.

Oropharyngeal Structure Resections and Consequences

Surgical resection(s) involving oral, pharyngeal, laryngeal, and esophageal structures commonly results in dysphagia. The actual functional deficits are dependent on the extent of the specific resection and the reconstructive procedure (36). New data, for example, have shown that patients with small resections of the oral tongue and tongue base had equal or better functional results with primary closure of the defect than with flap reconstruction (47). Additional data are needed to investigate the best method of closure for larger defects of the oral tongue and tongue base. Although this makes for a heterogeneous population (38), surgical resections nevertheless result in predictable patterns of dysphagia and aspiration risk (37). Common dysphagia symptoms are increased pooling of secretions, drooling, pocketing of food in the lateral and anterior sulci, difficulty with mastication, numbness, decreased temperature and pain sensation, and poor bolus control and transport.

Oral Cavity

Aspiration is not characteristic in patients with resections of the anterior tongue and floor of mouth, regardless of the type of closure (i.e., primary or flap). These patients have problems with the oral preparatory and oral phases of swallowing, but the pharyngeal phase is not disrupted, eliminating significant risk of aspiration (38).

However, resection of the lips, anterior tongue, and floor of mouth has social consequences for the individual. Drooling and bolus loss anteriorly make eating in public difficult and vigilance must be maintained to place the bolus posteriorly in the oral cavity to circumvent an anterior floor of mouth defect or loss of the tongue tip.

More extensive resections of the oral structures require a skin graft, tissue flap, or microvascular free flap. Generally, the larger the resection and subsequent reconstruction, the greater the probability of dysphagia and the higher the aspiration risk. McConnel et al. (48) compared three methods of oral reconstruction and found that the best method of reinstating masticatory and swallowing ability was intraoral skin grafting, followed by a myocutaneous flap and, last, a tongue flap. Microvascular free flaps have recently shown promise for oral cavity reconstructions that may surpass skin grafting (49).

Glossectomy

Total glossectomy results in a significant aspiration risk due to the obvious impairment of the oral preparatory and oral phases of swallowing and subsequent failure to trigger the swallowing reflex (50,51 and 52). When tumor is extensive and invades the preepiglottic space or the vallecula, it may be necessary to perform a total laryngectomy in conjunction with total glossectomy because of the high risk of life-threatening aspiration, especially in elderly and debilitated patients who are unable to tolerate the risk of recurrent aspiration (52).

Rehabilitation of the total glossectomy patient has focused on prosthetic management, with either a prosthetic tongue or palatal augmentation, to aid in deglutition and articulation (53,54 and 55).

Mandibulectomy

When cancer has invaded bone, a composite resection (i.e., glossectomy, mandibulectomy, and radical neck dissection) is performed for an en bloc resection. Oral preparatory and oral phases of swallowing are affected due to surgical changes in the muscles of the tongue and floor of mouth. Functional deficit is directly proportional to the amount of surgical resection, with the prognosis for prosthetic and functional rehabilitation better when more bone, musculature, and dentition are present postoperatively (56). When the anterior mandibular arch is resected, the genioglossus muscle, which composes the bulk of the tongue and suprahyoid laryngeal support, loses its insertion, resulting in drooling (57). If the mandible is cut, the inferior alveolar nerve, a sensory branch of V3, may be severed, resulting in ipsilateral anesthesia of mandibular dentition, alveolar ridge, labial alveolar mucosa, gingiva, skin, and mucous membrane of the lower lip, and skin of the chin; as well as reduced tactile sensation to the tongue. Bolus loss anteriorly and pocketing of food in the ipsilateral buccal sulcus often occur.

Palate: Hard and Soft

Palatal defects cause abnormalities in the oral preparatory and oral phases of swallowing. Hard palate defects are successfully handled with an obturator (58) that prevents food from entering the nose via the surgically created oronasal fistula. Soft palate defects are more difficult to solve, as the soft palate is a dynamic muscular structure. Resection often results in velopharyngeal insufficiency due to insufficient length for oronasal separation and neuromuscular deficits due to injury or severing of C-X. Lateral soft palate defects are more difficult to obturate than midline deficits (56). Both hard and soft palate defects and the obturator itself cause decreased sensation, which may impair oral function and result in dysphagia. More recent surgical restoration techniques have attempted to preserve sensation along with functional anatomical separation of the oral and nasal cavities by using nerve grafts and sensate flaps (49). Objective improvement in swallowing has not yet been demonstrated.

Pharynx and Esophagus

When the hypopharynx is involved with tumor, resection involves the pharynx and, by necessity, the larynx, secondary to life-threatening risk of aspiration. Reconstruction is undertaken by gastric pull-up, jejunal free flap with microvascular anastomosis, regional myocutaneous flap, colon interposition, or radial forearm free flap (37).

Similarly, if the tumor is extensive and involves the esophagus as well, a total pharyngolaryngoesophagectomy with gastric pull-up or jejunal interposition is necessary. Although aspiration cannot occur after these procedures, dysphagia can occur due to a fistula or, more likely, poor emptying of the gastric segment or jejunal graft because gravity must be relied on to transport material through a low-resistance tube. The patient presents with a “full” feeling at the base of tongue and oral regurgitation occurs if an upright posture is not maintained during and for at least an hour after eating (59).

Laryngectomy: Total and Partial

There are three distinct types of swallowing problems corresponding to total laryngectomy and partial laryngectomies (i.e., supraglottic and hemilaryngectomy). These are dysphagia secondary to pharyngeal or cricopharyngeal dysmotility (60), recurrent tumor, and benign stricture (61). Partial laryngectomies are performed to save at least one vocal fold for preservation of voice.

The incidence of dysphagia after total laryngectomy is highly variable, ranging from 10% to 58% (61,62 and 63). Dysphagia may be underestimated because retrospective analyses may not identify all patients with complaints of dysphagia (62) and because aspiration is eliminated by the surgical separation of the respiratory and digestive tracts. Nonetheless, total laryngectomy alters the swallowing mechanism because there can no longer be laryngeal elevation with the concomitant development of negative pressure in the pharyngoesophageal segment to aid in bolus propulsion. The laryngectomy therefore increases the propulsive pressure generated by the tongue (64). Fistulae may develop secondary to the increased swallowing pressures, especially due to increased mucosal edema in the immediate postoperative period.

It has been recommended that a cricopharyngeal myotomy be performed at the time of total laryngectomy to aid in bolus transit into and through the pharyngoesophageal segment (65). Also, hypopharyngeal stenosis is a relatively common occurrence after total laryngectomy (66) and is most likely due to the nature of the surgery rather than the site of the lesion (64). Dilatation is the most common therapy solution, but microvascular intestinal transfer grafts may be required.

Supraglottic laryngectomy involves resection, in the horizontal plane, of two of the three airway protective mechanisms, the epiglottis and aryepiglottic folds and false vocal folds (but not the true vocal folds), and often the hyoid bone, which provides skeletal support superiorly for the suspensory mechanism of the larynx (37,67). Supraglottic laryngectomy is organ-sparing surgery that places the patient at high risk for dysphagia and aspiration secondary to poor ability to protect the airway and reduced pharyngeal clearing resulting in aspiration after the swallow (67,68). Recovery of swallowing may take as little as 2 weeks, but some patients never regain functional swallowing. Although an overall failure rate between 8% and 20% was reported (37), the median number of days to resumption of successful oral intake was 106 (68).

Partial laryngectomy involves excision, in the vertical plane, of the aryepiglottic fold, false vocal fold, and true vocal fold unilaterally, sparing the epiglottis (37). Specific oncologic requirements may also necessitate resections involving the hyoid bone, arytenoid cartilage, superior laryngeal nerve, thyroid cartilage, or base of tongue, with concomitant increasing swallowing difficulties based on the extent of surgery.

Most patients exhibit some amount of aspiration in the short term after partial laryngectomy, ranging from 50% to 67% (37). Although life-threatening complications (e.g., pulmonary fibrosis, pneumonia, and lung abscess) can develop, most patients eventually regain the ability to eat by mouth after surgical resection, reconstruction,

and dysphagia rehabilitation (69,70).

Tracheotomy and Tracheotomy Tubes

Dysphagia has been shown to be a problem in both the head and neck cancer and tracheotomized populations. It appears that alterations in oral, pharyngeal, and laryngeal anatomy and physiology secondary to either the cancer and surgical resection and reconstruction or changes secondary to bypassing the upper airway with a tracheotomy place each of these populations at risk for various swallowing difficulties, including aspiration. When the populations overlap, as in patients with both head and neck cancer and a tracheotomy, the incidence of aspiration increases (33).

Tracheotomy has become one of the most frequently performed operations in otolaryngology head and neck surgery (71,72) due to the wide variety of conditions for which it is performed (e.g., acute airway obstruction secondary to infection or edema, chronic airway obstruction secondary to a mass or sleep apnea, respiratory difficulties requiring prolonged ventilatory support or to bypass the dead space of the upper airway, and chronic aspiration) (72). Despite such widespread use, the effect of a tracheotomy on the involved anatomical structures and their physiological relationships is not without consequences.

In humans, the two diverse and mutually exclusive functions of deglutition and respiration share the same anatomical structures in the upper aerodigestive tract. Swallowing is a highly complex activity requiring precise coordination between anatomical structures and the sequencing of physiological events occurring within a closed aerodigestive system. Tracheotomy inherently violates the closed aerodigestive system and alters the precise interrelated coordination involved in breathing and swallowing (71). Glottic reflexes have been shown to be less sensitive in experimental animals after tracheotomy (73,74).

Explanations as to the cause of aspiration after tracheotomy and placement of a tracheotomy tube include the following:

1. Fixation of the larynx, causing impaired mechanical ability of the supraglottic larynx to achieve closure and protect the airway by limiting the rostrocaudal excursion of the laryngotracheal complex (71,75,76 and 77)
2. Esophageal compression caused by a distended trachea secondary to an inflated tracheotomy tube cuff (78,79)
3. Desensitization of the larynx secondary to diversion of normal airflow through the tracheotomy (71,76)
4. Neurophysiological changes, specifically, adductor vocal fold dysfunction and a weakened closure response after long-term tracheotomy
5. Alterations in respiratory abductor function of the larynx secondary to bypassing the upper airway via tracheotomy (71,73,74)

Tracheotomy tube occlusion status, as it relates to prevalence of aspiration in head and neck cancer surgical patients, is unclear. A case study (75) reported that the presence of an open tracheotomy tube appeared to have an adverse effect on swallowing; on plugging and subsequent removal of the tube, the dysphagia resolved. Although tracheotomy caused neurophysiological changes in both abductor and adductor laryngeal responses, when the tracheotomy cannula was occluded for 3 minutes, some motor return was observed (71,74). Muz and colleagues reported on patients with tracheotomy and head and neck cancer. They found that aspiration increased when the tracheotomy tube was unoccluded (80) and that aspiration occurred twice as often with an unoccluded tube (33).

In contrast to these findings, when the occlusion status of the tracheotomy tube in head and neck cancer patients was altered, in no case did an early, postsurgical head and neck cancer subject aspirate first with an occluded tracheotomy tube and then not aspirate with an unoccluded tube or, conversely, not aspirate with an occluded tube and then aspirate when the tube was occluded (81). It was concluded, therefore, that short-term (i.e., approximately 5 minutes) tracheotomy tube occlusion status in early postsurgical head and neck cancer patients did not influence the prevalence of aspiration. It would be of great interest to investigate the impact of long-term tracheotomy use and tube occlusion in humans to determine whether tracheotomy tube occlusion alters the pattern of laryngeal reflexes.

There are a number of possible reasons for the disagreement regarding aspiration results between the early and late postsurgical cancer patients. First, a larger number of consecutive patients were used (81) than the observations reported previously (80). Second, any bias to finding aspiration was eliminated because no selection process determined referral for dysphagia evaluations (81) as was the case in a follow-up study (33). Third, early postsurgical patients (81) may exhibit dysphagia patterns that are different from those of late postsurgical patients (33,80) as a result of the length of time a tracheotomy tube is present, early postoperative edema, more impaired lingual and mandibular range of motion, and greater oropharyngeal sensitivity and pain. Fourth, it is also understood that physiological impairment of adductor laryngeal reflexes may not occur for 6–8 months after tracheotomy (74). Fifth, differences in the bolus volumes used, specifically 5 ml (81) and 10 ml in the scintigraphy studies (33,80), could have influenced aspiration results.

A Comment on Tracheotomy, Tracheotomy Tube Placement, and Aspiration Status

The reader may draw the conclusion from the preceding discussion dealing with aspiration, surgical tracheotomy, and tracheotomy tubes that the latter two variables are causal factors for the outcome (i.e., aspiration). This, however, may not be the case. A basic flaw in this literature is the lack of pretracheotomy swallowing assessment results. There is no way to tell who will receive a tracheotomy in the future, and therefore, once a tracheotomy is performed, the pretracheotomy swallow can, ipso facto, never be assessed. There are a number of reasons for this. Many patients are orally intubated before a scheduled tracheotomy, precluding a swallowing evaluation. Cancer surgery alters head and neck anatomy and physiology, predisposing these patients to increased aspiration risk with or without a concomitant tracheotomy. Finally, pretracheotomy swallowing evaluations done for elective tracheotomy (e.g., sleep apnea) are not routinely performed.

Recent research has shown that the pretracheotomy swallowing status of most patients who had a tracheotomy did not change. In other words, patients who aspirated before their tracheotomy continued to aspirate and patients who swallowed successfully before tracheotomy continued to do so after undergoing tracheotomy. No causal relationship between tracheotomy and aspiration status was exhibited. Rather than tracheotomy, the patient's medical status, neurological functioning, and head and neck cancer were the primary determinants of swallowing success (82).

External Beam Radiation Therapy

Although EBRT does not usually cause physiologically based swallowing problems, reduced oral and pharyngeal swallowing performance, as demonstrated by longer oral transit times, lower oropharyngeal swallow efficiency, increased pharyngeal residue, and reduced cricopharyngeal opening duration, have been reported (83). As is the case after surgery and reconstruction, a wide variety of oral complications contributing to poor oral intake can occur (84). Complications may become more prevalent when combined treatments are used (e.g., surgery with EBRT) whether given pre- or postoperatively (85). Some problems are temporary [e.g., mucositis, infections, odynophagia, trismus, and dysgeusia (86)] and resolve in the months after completion of EBRT. Other problems (e.g., xerostomia, dental caries, osteonecrosis, and tissue necrosis) may be permanent (87).

Chemotherapy

Similar to EBRT, chemotherapy does not usually cause physiologically based swallowing problems, but it does contribute to poor oral intake due to the emergence of taste changes (84). In addition, the cytotoxic effects of chemotherapeutic agents can cause mucositis, xerostomia, increased dental caries, nausea, vomiting, and dysgeusia. More severe complications can lead to life-threatening hemorrhage and infections, which are more likely to occur in a chemotherapy patient than in an EBRT patient (88).

COUNSELING

Preoperative counseling is often quite helpful, not so much to discuss the extent of the upcoming surgery but to prepare the patient for possible swallowing problems and, if they occur, to assure the patient that rehabilitation will be initiated before discharge from the hospital. The use of a nasogastric tube for nutritional maintenance immediately postoperatively and the possibility of a feeding gastrostomy tube if dysphagia persists are discussed. The patient is informed that swallowing diagnostics and rehabilitation will most likely begin before the nasogastric tube is discontinued. The different types of food consistencies (i.e., thin and thick liquid, puree, soft/moist solid, and hard/dry solid) are discussed, and the patient should understand that a diet may be restricted to one or more of the consistencies, depending on postoperative swallowing ability.

Postoperative counseling deals with long-term issues related to nutritional maintenance, type of food consistency (e.g., restriction to a blenderized diet), and the importance of following swallowing recommendations and therapy exercises after discharge from the hospital. If postoperative EBRT or chemotherapy is to be given, the patient is educated regarding possible consequences (i.e., xerostomia, localized edema, odynophagia with EBRT and mucositis and taste changes with chemotherapy), to decrease anxiety and concern should these side effects occur.

DIAGNOSTICS

Dysphagia diagnostics has three purposes:

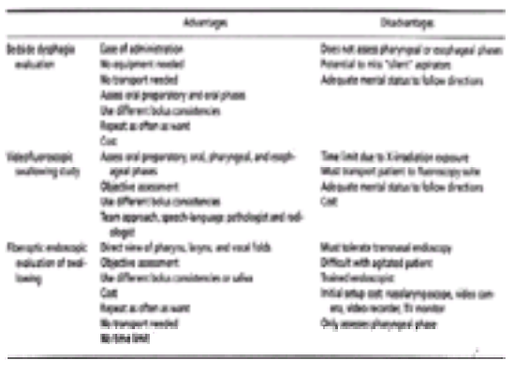
1. To document if dysphagia and aspiration are present
2. To determine why dysphagia and aspiration occurred
3. To make recommendations for rehabilitation strategies (e.g., bolus consistencies, head positions, and swallowing techniques)

The bedside dysphagia evaluation (BDE), which follows a standardized protocol, examines the oral preparatory and oral phases of swallowing and can identify patients at risk for dysphagia (89). The accuracy of such predictions, however, was reported to range from 42% (90) to 66% (91). Despite such variable accuracy, the BDE is widely used in making the initial diagnosis of dysphagia and subsequent recommendations for oral feeding.

The videofluoroscopic swallowing study (VFSS) (92) uses a more extensive test protocol than the original modified barium swallow (2) and is the gold standard for diagnosing dysphagia and recommending rehabilitation. Performed in a fluoroscopy suite, it assesses all four phases of swallowing, and many studies over the past decade have shown it to have excellent sensitivity and specificity (89).

The flexible endoscopic evaluation of swallowing (FEES) (93,94) is a relatively new bedside procedure for assessing the pharyngeal phase of swallowing by using a flexible nasolaryngoscope for visualization of the pharynx and larynx on a video monitor. Objective information can be obtained regarding aspiration, safety of oral feeding, bolus consistency, and optimum positioning in patients for whom a BDE is inadequate or deemed unreliable, and when a VFSS is difficult or impossible to perform.

The relative advantages and disadvantages of the BDE, VFSS, and FEES diagnostic procedures are listed in Table 12-3.



	Advantages	Disadvantages
Bedside dysphagia evaluation	Ease of administration No equipment needed No transport needed Assess oral preparatory and oral phases Use different bolus consistencies Repeat as often as want Cost	Does not assess pharyngeal or esophageal phases Potential to miss "silent" aspirators Adequate mental status to follow directions
Videofluoroscopic swallowing study	Assess oral preparatory, oral, pharyngeal, and esophageal phases Objective assessment Use different bolus consistencies Team approach, speech-language pathologist and radiologist	Time limit due to X-irradiation exposure Must transport patient to fluoroscopy suite Adequate mental status to follow directions Cost
Fiberoptic endoscopic evaluation of swallowing	Direct view of pharynx, larynx, and vocal folds Objective assessment Use different bolus consistencies or saliva Cost Repeat as often as want No transport needed No time limit	Must tolerate transnasal endoscopy Difficult with agitated patient Trained endoscopist Initial setup cost: nasolaryngoscope, video camera, video recorder, TV monitor Only assesses pharyngeal phase

TABLE 12-3. RELATIVE ADVANTAGES AND DISADVANTAGES OF THE BEDSIDE DYSPHAGIA EVALUATION, VIDEOFLUOROSCOPIC SWALLOWING STUDY, AND FIBEROPTIC ENDOSCOPIC EVALUATION OF SWALLOWING PROCEDURES

DIAGNOSTICS WITH SPECIAL POPULATIONS

Tracheotomy Tubes

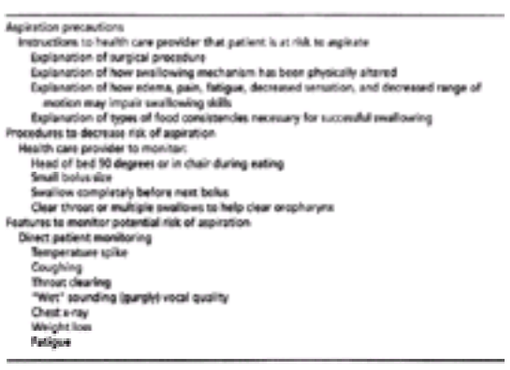
When assessing swallowing with a tracheotomized patient, the tracheotomy cuff should always be deflated. The reason for this is that an inflated cuff does not prevent aspiration but only delays its detection. Recent evidence has demonstrated that the occlusion status of the tracheotomy tube does not influence the prevalence of aspiration, but rather age (>65 years) and overall medical condition predispose the patient for aspiration (81,82,95,96). The deflated cuff allows for immediate identification of aspiration, by either coughing of a food bolus out the tracheotomy tube or evidence of food in the trachea after tracheal suctioning. An inflated tracheotomy cuff does not prevent aspiration (by definition, aspiration has occurred when the bolus is below the true vocal folds) and only delays evidence of aspiration for a short time (i.e., until the aspirated material that has collected just above the cuff migrates between the cuff and tracheal wall and enters the main stem bronchi and lungs).

Ventilator Dependency

Patients on ventilatory support can eat orally. However, because the tracheotomy cuff cannot be deflated, extra care must be taken during dysphagia diagnostics and subsequent rehabilitation. A careful BDE in conjunction with FEES should be capable of determining the swallowing ability and bolus consistency necessary for successful oral feeding.

RECOMMENDED ORAL FEEDING

Once the speech-language pathologist has reviewed the medical history, completed a physical assessment of the swallowing mechanism, and performed a diagnostic dysphagia evaluation, determination of type of oral feeding (if any) can be made. The speech-language pathologist then makes recommendations regarding food consistencies, rehabilitation techniques, aspiration precautions, and criteria for discontinuing oral feedings due to signs of aspiration (Table 12-4).



Aspiration precautions
Instructions to health care provider that patient is at risk to aspirate
Explanation of surgical procedure
Explanation of how swallowing mechanism has been physically altered
Explanation of how edema, pain, fatigue, decreased sensation, and decreased range of motion may impair swallowing skills
Explanation of types of food consistencies necessary for successful swallowing
Procedures to decrease risk of aspiration
Health care provider to monitor:
Head of bed 90 degrees or in chair during eating
Small bolus size
Swallow completely before next bolus
Clear throat or multiple swallows to help clear oropharynx
Features to monitor potential risk of aspiration
Direct patient monitoring
Temperature spike
Coughing
Throat clearing
"Wet" sounding (gurgly) vocal quality
Chest x-ray
Weight loss
Fatigue

TABLE 12-4. COMMON ASPIRATION PRECAUTIONS, PROCEDURES TO DECREASE RISK OF ASPIRATION, AND FEATURES TO MONITOR POTENTIAL ASPIRATION RISK FOR HEALTH CARE PROVIDERS

Individualized aspiration precautions, recommended techniques to improve dysphagia, and the steps to be followed for successful swallowing are often placed at the head of the bed on brightly colored paper so that all health care providers are alerted to the fact that a swallowing problem exists. As noted in the previous paragraph, Table 12-4 lists common aspiration precautions, procedures to decrease aspiration risk, and features that health care providers should be cognizant of when monitoring the dysphagic individual both during and after eating.

Specific indirect, direct, compensatory, and adaptive rehabilitative strategies are listed in Table 12-5. Indirect strategies do not use a food bolus, and the exercises are focused on improving range of motion and strength of the structures of the swallowing mechanism, from labial closure to airway protection. Direct strategies use a food bolus consistency and quantity that are safe for the patient and direct him or her regarding optimal bolus placement in the oral cavity and specific instructions regarding postures and positioning. Compensatory strategies encompass bolus consistency modifications and steps to be followed for a successful swallow. Adaptive strategies use devices to aid in successful swallowing by optimal bolus placement, manipulation, and transit in the oral cavity (see reference 97 for a detailed discussion of oral

and oropharyngeal prostheses used to rehabilitate and facilitate swallowing skills).

TABLE 12-5. INDIRECT, DIRECT, COMPENSATORY, AND ADAPTIVE REHABILITATION STRATEGIES FOR DYSPHAGIA

The following is an example of dysphagia rehabilitation for a patient with decreased lingual range of motion secondary to lingual resection. Indirect and direct dysphagia rehabilitation (Table 12-5) was attempted first, but lingual motion remained decreased and food pocketed in the left sulcus. The speech-language pathologist and maxillofacial prosthodontist collaborated on designing a prosthesis to aid in swallowing. The puree bolus consistency was placed on the right side of the oral cavity by a long-handled spoon, with the patient's head tilted to the right. The custom-made palatal prosthesis physically lowered the palatal vault to allow for tongue contact. More normal oral preparatory and oral phases of swallowing were thus achieved. The patient was instructed to swallow twice to clear any residual bolus from the oropharynx. This rehabilitation strategy resulted in a successful swallow.

SUPRAGLOTTIC SWALLOW

The supraglottic swallow is a technique with the goal of adducting the true vocal folds to protect the airway during swallowing. The technique can also be used by patients who have poor vocal fold adduction secondary to tumor involvement or surgical resection of the laryngeal branches of C-X (i.e., the superior laryngeal nerve and right and left recurrent laryngeal nerves), neurological insult, or partial laryngectomy (68). The supraglottic swallow is composed of the following five steps:

1. Adduct true vocal folds and hold breath (tense neck).
2. Swallow during breath hold.
3. Clear throat or cough vigorously immediately after the swallow; do not inhale at this time.
4. Adduct true vocal folds and hold breath again.
5. Swallow again during breath hold.

PHARYNGEAL AND ESOPHAGEAL PHASE DYSPHAGIA

There is no direct therapy to improve decreased pharyngeal wall motion or paralysis, cricopharyngeus dysfunction, or esophageal phase disorders. Pharyngeal phase problems that may indirectly benefit from rehabilitation are stimulation of the swallow reflex, reduced laryngeal closure, and paralysis by compensatory head positions. Other pharyngeal phase disorders [e.g., cervical osteophyte (98), scar tissue, and cricopharyngeus dysfunction (71,99)] are treated surgically. Esophageal phase disorders are treated both surgically and medically (99,100).

CONCLUSIONS

Successful eating and swallowing are prerequisites for a normal life. Not only does dysphagia impair the individual's quality of life, but if aspiration does occur, the consequence could be life-threatening pneumonia. The patient should be counseled that although the cancer or its treatment may cause dysphagia, there are intervention strategies available to make eating as pleasant and successful an experience as possible.

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13

CHEMOTHERAPY-RELATED NAUSEA AND VOMITING

ANN M. BERGER
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NATURE OF THE PROBLEM

Chemotherapy-induced nausea and vomiting is one of the most feared effects of cancer treatment. The incidence and severity of nausea or vomiting in patients receiving chemotherapy varies depending on the type of chemotherapy given, dose, schedule, combinations of medications, and individual characteristics. Approximately 70–80% of all patients who receive chemotherapy experience nausea and vomiting (1,2). Anticipatory nausea and vomiting are experienced by approximately 10–44% of patients who receive chemotherapy (3,4,5 and 6).

The phenothiazines were the mainstay of antiemetic agents before the mid-1970s (7,8). Currently, there are many efficacious antiemetic regimens for the nausea and vomiting produced by chemotherapeutic agents (9). In a study conducted in 1983, cancer patients ranked nausea and vomiting as the first and second most severe side effects of chemotherapy, respectively (10). After the emergence of new antiemetic agents and alterations in chemotherapeutic regimens, patients' perceptions of the most severe side effects were modified. In a 1993 study, 155 cancer patients receiving chemotherapy reported that they experienced an average of 20 physical and psychosocial symptoms. Nausea was ranked as the most severe symptom and vomiting as the fifth (11). Therefore, nausea is also an important efficacy parameter when evaluating an antiemetic.

Use of these new antiemetic agents has decreased the incidence and severity of nausea and vomiting induced by chemotherapy. However, these agents have not totally prevented the problem. The consequences of not controlling nausea and vomiting induced by cancer treatment may lead to medical complications, a failure of the patient to comply with the cancer therapy and follow-up, and a diminished quality of life.

PATHOPHYSIOLOGY OF NAUSEA AND VOMITING

The precise mechanisms by which chemotherapy induces nausea and vomiting are unknown. However, it appears probable that different chemotherapeutic agents act at different sites and that some chemotherapeutic agents act at multiple sites (12). The fact that different chemotherapeutic agents cause nausea and vomiting by different mechanisms and that one chemotherapeutic agent may induce nausea and vomiting by more than one mechanism helps us to understand why there is no one antiemetic regimen that is effective all of the time.

Mechanisms by which chemotherapeutic agents cause nausea and vomiting are activation of the chemoreceptor trigger zone (CTZ) either directly or indirectly; peripheral stimulation of the gastrointestinal (GI) tract; vestibular mechanisms; cortical mechanisms; or alterations of taste and smell (Table 13-1). For the majority of the chemotherapeutic agents, the most common mechanism is thought to be activation of the CTZ.

Stimulation of chemoreceptor trigger zone
Peripheral mechanisms
Damage of gastrointestinal mucosa
Stimulation of gastrointestinal neurotransmitter receptors
Cortical mechanisms
Direct cerebral activation
Indirect (psychogenic) mechanisms
Vestibular mechanisms
Alterations of taste and smell

From Berger AM, Clark-Snow RA. Adverse effects of treatment. In: DeVita VT Jr, Hellman S, and Rosenberg SA, eds. *Cancer: principles and practice of oncology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2001, with permission.

TABLE 13-1. MECHANISMS OF NAUSEA AND VOMITING AFTER CHEMOTHERAPY

The CTZ is located in the area postrema of the brain and can be reached by emetogenic chemicals via the cerebrospinal fluid or the blood. The thought is that the mechanisms of interaction between the CTZ and chemotherapy involve the release of various neurotransmitters that activate the vomiting center. Either one or a combination of these transmitters may induce vomiting. Some of the neurotransmitters located in the area postrema of the brain that may be excited and lead to emesis include dopamine, serotonin, histamine, norepinephrine, apomorphine, neurotensin, angiotensin II, vasoactive intestinal polypeptide, gastrin, vasopressin, thyrotropin-releasing hormone, leucine-enkephalin, and substance P (13). Other enzymes surround the CTZ, such as adenosine triphosphatase, monoamine oxidase, cholinesterase, and catecholamines. However, their role in chemotherapy-induced emesis is unknown.

Until recently, the neurotransmitter that appeared to be the most responsible for chemotherapy-induced nausea and vomiting was dopamine. Many effective antiemetics are dopamine antagonists that may bind specifically to the D_2 receptor. However, there is a high degree of variation in dopamine receptor binding affinity by these drugs (14). The action of some drugs that cause nausea and vomiting is affected very little or not at all by dopamine antagonists. It is known that not all the important receptors in the CTZ are dopaminergic, as the effect of dopamine antagonists is not equal to surgical ablation of the CTZ (15). It has also been noted that the degree of antiemetic activity of high-dose metoclopramide cannot be explained on the basis of dopamine blockade alone (16).

Histamine receptors are found in abundance in the CTZ. However, H_2 antagonists have no antiemetic activity. H_1 antagonists alleviate nausea and vomiting induced by vestibular disorder and motion sickness but not nausea and vomiting induced by chemotherapy (17,18).

Knowledge that opiate receptors are found in abundance in the CTZ, as well as the fact that narcotics have mixed emetic and antiemetic effects that are blocked by naloxone, and that naloxone has emetic properties, have led to the proposal of opiates or enkephalins as an antiemetic. High doses of naloxone augments emesis induced by chemotherapy, and low doses of narcotic may reduce emesis (19). Studies to date have shown that opiates can prevent chemotherapy-induced emesis in laboratory animals. However, both butorphanol and buprenorphine have not proven to be effective antiemetics in patients who received previous chemotherapy (20,21). One study by Lissoni et al. (22) did demonstrate that Fk-33-824 was more effective as an antiemetic in patients who received cisplatin; however, it was ineffective for patients receiving cyclophosphamide or epirubicin.

Edwards et al. (23) found that arginine vasopressin levels rise to a greater extent in patients who vomit when they receive chemotherapy as compared to those who do not vomit. It has been suggested that perhaps arginine vasopressin plays a role in nausea more than in the vomiting induced by chemotherapy. Dexamethasone, which is a known effective antiemetic, may work by reducing arginine vasopressin levels (24). Another mechanism of action of corticosteroids as antiemetics may be related

to modulation of prostaglandin release (25).

Some evidence suggests that although no one neurotransmitter is responsible for all chemotherapy-induced nausea and vomiting, it appears that serotonin and 5-hydroxytryptamine (5-HT) receptors are particularly important in the pathophysiology of acute vomiting, whereas others may be more important in the pathophysiology of nausea and delayed emesis. The role of the 5-HT type 3 (5-HT3) receptor in chemotherapy-induced emesis was recognized by examining the mechanism of action of high-dose metoclopramide in decreasing cisplatin-induced emesis. High-dose metoclopramide, unlike other D_2-receptor antagonists, has an exceptionally good capacity to decrease the emesis induced by cisplatin administration (26). It has been recognized that metoclopramide has pharmacological effects other than dopamine antagonism. Metoclopramide is a weak antagonist of peripheral 5-HT3 receptors (27) and can stimulate GI motility by increasing acetylcholine release from the cholinergic nerves of the GI tract (28). To test whether 5-HT3-receptor blockade would decrease cisplatin-induced emesis, Miner and Sanger (29) took a substituted benzamide, BRL 24924, which has stimulatory effects on the GI tract and is a 5-HT3-receptor blocker, and demonstrated decreased emesis in ferrets that received cisplatin. This study was repeated with a nonbenzamide, selective 5-HT3-receptor blocker MDL 72222, which has no GI-stimulating activity. The study revealed that cisplatin-induced emesis was totally blocked by this compound (30). The same conclusion was reached in another study using a different nonbenzamide, the selective 5-HT3 antagonist ICS 205-930 (31). These studies demonstrated the role of 5-HT3-receptor blockade in chemotherapy-induced emesis.

The precise mechanism of action of the 5-HT-receptor antagonists is unknown. However, they may have both a central and a peripheral effect. The GI tract contains 80% of the body's supply of serotonin. It has been suggested that perhaps chemotherapy administration causes release of serotonin from the enterochromaffin cells of the GI tract, which then stimulates emesis via both the vagus and greater splanchnic nerve as well as stimulating the area postrema of the brain. After cisplatin administration, there is an increase in urinary excretion of 5-hydroxyindoleacetic acid, the main metabolite of serotonin. This increase parallels the number of episodes of emesis (32). Studies have shown that the 5-HT3-receptor antagonists decrease emesis from several chemotherapeutic agents, including cisplatin, cyclophosphamide, and doxorubicin (33,34,35 and 36).

There has been new evidence regarding the potential role of substance P in emesis and new data about the use of neurokinin (NK1) antagonists in the management of emesis. Substance P, a neuropeptide found in the GI tract and the CTZ of the area postrema, exerts its emetic effects by binding to a specific neuroreceptor, NK1. A number of compounds that selectively block NK1 have been identified. These NK1 antagonists demonstrate a wide spectrum of antiemetic activity against numerous emetic stimuli in animal models, including several emetic stimuli that are not affected by serotonin and dopamine receptor antagonists. Studies in preclinical models have demonstrated that several NK1 antagonists have activity in the prevention of both acute and delayed cisplatin-induced nausea and vomiting. Two randomized double-blind studies have demonstrated that NK1 antagonists are beneficial in the prevention of delayed emesis (37,38). These agents may also provide additional benefit in the prevention of acute nausea and vomiting when combined with a 5-HT3 antagonist and dexamethasone.

The second most important mechanism whereby chemotherapy may induce emesis is peripheral effects that are thought to arise from the pharynx and the upper GI tract. Most likely, the chemotherapy does not directly stimulate the peripheral receptors. Rather, neurotransmitters probably are released as a result of local GI irritation or damage. GI-tract serotonin, dopamine, opiate, histamine, and cholinergic receptors are most likely involved in the emesis induced by chemotherapy. The peripheral effects may be abolished by vagotomy, indicating that impulses from the GI tract may reach the vomiting center via the vagus and sympathetic nerves (39).

Another mechanism that may be involved in chemotherapy-induced emesis could be the therapy's effect on the vestibular system. It is known that patients who have a history of motion sickness experience a greater severity, frequency, and duration of nausea and vomiting from chemotherapy than patients who do not experience motion sickness. The mechanism by which the vestibular system may lead to chemotherapy-induced emesis is unknown. However, it is postulated that sensory information that is received by the vestibular system is different from information that was expected (40).

Some investigators believe that taste changes induced by chemotherapy may lead to nausea and vomiting. Some chemotherapeutic agents, such as cisplatin or gallium nitrate, can lead to loss of taste sensation or to a metallic taste in the mouth. A study conducted with patients receiving chemotherapy for malignant melanoma revealed that patients developed a more intense sense of taste for sweet, bitter, sour, and salt. After chemotherapy, the patients rated the highest concentration of sweet as lower, and the patients' discrimination between highest and lowest concentrations of sour, bitter, and sweet was decreased (41). In another study of patients with breast carcinoma who received cyclophosphamide, methotrexate, and 5-fluorouracil, 36% reported a bitter taste in their mouth. One-third of the patients thought that the bitter taste caused vomiting (42). The exact mechanism by which taste is changed by chemotherapy is unknown. However, it is thought that while the drugs are in the plasma or saliva, they have a direct effect on the oral mucosa or taste buds. Changes in taste may contribute both to nausea and vomiting as well as to anorexia.

Finally, chemotherapy-induced emesis may be induced by direct or indirect effects on the cerebral cortex. Animal studies have shown that nitrogen mustard partially causes emesis via direct stimulation of the cerebral cortex (43). Studies demonstrate that the risk of nausea and vomiting is increased when a patient's roommate is experiencing nausea and vomiting. It is also known that the amount of sleep before receiving chemotherapy may influence whether a patient develops chemotherapy-induced emesis. In addition, large differences exist in the severity and incidence of nausea and vomiting from the same chemotherapeutic agents in different countries (44). These studies indicate that indirect psychological effects can mediate chemotherapy-induced nausea and vomiting.

Aside from there being more than one mechanism by which each chemotherapeutic agent may induce emesis, chemotherapy induces emesis in a manner different from that of other classic emetic agents. Drugs such as apomorphine, levodopa, digitalis, pilocarpine, nicotine, and morphine cause vomiting almost immediately. Nitrogen mustard also may lead to emesis immediately. However, most chemotherapeutic agents and radiotherapy require a latency period before emesis begins. Also, most chemotherapeutic agents do not induce emesis in a monophasic way, as do the classic emetic agents. Chemotherapeutic agents induce emesis with a delayed onset, and the emesis has multiphasic time courses (45). When managing chemotherapy-induced emesis, one should realize that there is most likely more than one mechanism involved, suggesting that there will not be one antiemetic regimen that will work for all patients all of the time.

EMETIC SYNDROMES

Patients undergoing therapy for the treatment and possible cure of cancer with chemotherapy often are faced with the distressing side effects of nausea and vomiting. Although advances in the 1990s have provided the clinician with an array of antiemetics and varied regimens, therapy-induced nausea and vomiting have yet to be totally eliminated. The goals of antiemetic therapy are as follows:

1. To achieve complete control in all settings
2. To provide maximum convenience for patients and staff
3. To eliminate potential side effects of the agents
4. To minimize the cost of treatment with antiemetic agents and drug administration

Five distinct but related emetic syndromes have been identified: acute chemotherapy-induced emesis, delayed emesis, breakthrough nausea and vomiting, refractory emesis, and anticipatory emesis. Traditionally, acute nausea and vomiting are defined as occurring within the first 24 hours after administration of chemotherapy. Delayed nausea and vomiting have been arbitrarily defined as occurring 24 hours after chemotherapy administration. More recent observations of the pattern of emesis indicate that delayed emesis may begin as early as 16 hours after chemotherapy administration and that serotonin may not be the primary mediator of symptoms for delayed emesis. Breakthrough nausea and vomiting are nausea and vomiting that occur despite preventive therapy. Rescue therapy is the treatment administered to patients who have not responded to the prophylactic regimens prescribed for acute or delayed nausea and vomiting. Refractory emesis occurs during subsequent cycles when antiemetic prophylaxis or rescues (or both) have failed in earlier cycles.

Anticipatory vomiting is a learned or conditioned response that typically occurs before, during, or after the administration of chemotherapy. Patients receiving one or a combination of several of the chemotherapy agents must receive an antiemetic regimen that is tailored to the individual pattern and emetic potential of each agent. For example, patients receiving a combination of high doses of intravenous cyclophosphamide and doxorubicin (Adriamycin) would require antiemetic coverage for the early onset of emesis usually seen with doxorubicin, as well as continued protection from cyclophosphamide-induced emesis that does not begin until 9–18 hours after the drug's administration (46). If patients are given the opportunity to receive the optimal antiemetic regimen during their initial course of chemotherapy, the likelihood of developing anticipatory emesis with subsequent cycles is greatly reduced. Other advantages for patients include increased tolerance of dose-intensified chemotherapeutic regimens. In addition, through the prevention of emesis, patients are able to achieve an enhanced quality of life at a particularly difficult time.

Two reports, one by Hesketh et al. (47) and an expert consensus by the American Society of Health-System Pharmacists, (48) contain new guidelines for the classification of the acute emetogenicity of chemotherapy into five levels (Table 13-2). When the agents are combined, ratings are based on the combined emetogenicity of the individual agents. An algorithm for defining the emetogenicity of combination chemotherapy has been developed (Table 13-3).

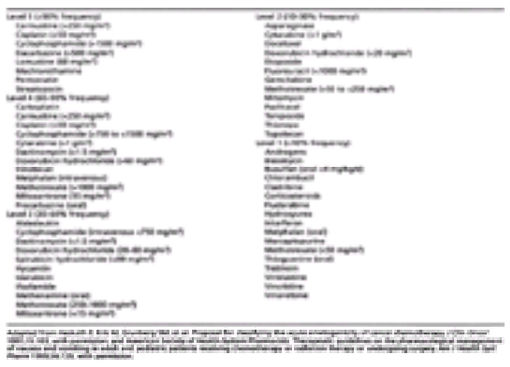

TABLE 13-2. EMETIC POTENTIAL OF CHEMOTHERAPEUTIC AGENTS

The most highly emetogenic agent in the chemotherapeutic combination must first be identified.
Level 1 chemotherapeutic agents do not contribute to the emetogenicity of the regimen.
Adding one or more level 2 chemotherapeutic agents increases the emetogenicity of the combination by one level greater than the most emetogenic agent in the combination.
Adding level 3 and 4 agents increases the emetogenicity of the combination by one level per agent.

Adapted from Hesketh P, Kris M, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997;15:103, with permission; and American Society of Health-System Pharmacists. Therapeutic guidelines on the pharmacological management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. *Am J Health Syst Pharm* 1999;56:729, with permission.

TABLE 13-3. RULES FOR IDENTIFYING THE EMETOGENICITY OF COMBINATION CHEMOTHERAPY

CONTROL OF EMESIS AND PATIENT CHARACTERISTICS

The methodology used in antiemetic studies has identified several useful patient characteristics and prognostic factors that may affect antiemetic control. These indicators become important for tailoring antiemetic regimens as well as designing antiemetic trials. Careful studies have defined previous experience with chemotherapy, alcohol intake history, age, and gender as influencing patient outcomes.

A patient's prior exposure to chemotherapy very often determines success or failure in controlling emesis with future treatment courses. Administration of the appropriate antiemetic during an initial course of chemotherapy can very often eliminate or significantly reduce the development of anticipatory emesis, in addition to decreasing the severity of delayed emesis.

Chronic and heavy alcohol usage—defined as more than 100 g of alcohol or five mixed drinks per day, whether in the past or currently—has been shown positively to affect the control of emesis. Ninety-three percent of patients in a prospective study who had a history of high alcohol intake were able to achieve a complete response, or no emesis, after receiving high doses of cisplatin with a combination antiemetic regimen (49). The hypothesis is that chemotherapy-induced emesis may be decreased in patients with a high alcohol intake because of “burnout” of the CTZ. Although emesis may be easier to control in this setting, patients nonetheless must receive an appropriate and effective antiemetic regimen. As a result, this prognostic factor has been incorporated in many prospective trials for stratification purposes.

Age as a prognostic factor cannot predict patient response to antiemetic therapy. Some studies have indicated better control in older patients, although others have reported little difference among various age groups. Age is, however, an important factor in determining the potential for the occurrence of acute dystonic reactions. Patients 30 years and younger are more prone to experience the acute dystonic reactions associated with the dopamine-receptor blocking agents, such as the phenothiazines, butyrophenones, and substituted benzamides. These side effects are usually characterized by trismus or torticollis. It is also important to remember that within this population of patients, chemotherapeutic agents that might necessitate antiemetics often are given over several consecutive days, increasing the possibility of the occurrence of acute dystonic reactions (50). A distinct advantage for the use of the serotonin or 5-HT3-blocking antiemetic agents is that they do not cause acute dystonic reactions, making them an especially beneficial treatment option for children and younger adults.

It has been difficult to explain the rationale for poorer control of emesis in some women receiving treatment for various malignancies. A possible explanation may be that women characteristically receive chemotherapeutic regimens that contain highly emetogenic agents, such as cisplatin and cyclophosphamide, usually given in combination, and are less likely than men to have a history of a high alcohol intake. Although these may be contributing factors, multivariate analyses in some larger studies have indicated that gender is an independent consideration that must be recognized in planning and analyzing clinical studies.

Other factors also have been reported possibly to affect the incidence of nausea and vomiting after chemotherapy. A patient may develop nausea and vomiting if he or she is anxious during the chemotherapy infusion, there is an expectation of severe side effects, or the patient's roommate is experiencing nausea and vomiting. Patients who are well motivated and have a good performance status may experience a decreased incidence of nausea and vomiting (51,52). Food intake before chemotherapy and the amount of sleep a patient has had may influence the degree of nausea and vomiting (53). Patients who are more likely to develop nausea and vomiting are those who have had severe emesis during pregnancy (54) and those who are prone to motion sickness (Table 13-4) (55,56).

Patient-specific factors
Previous emesis experience with chemotherapy
Alcohol intake
Age
Gender
Anxiety
Expectation of severe side effects
Roommate experiencing nausea and vomiting
Motivation level
Performance status
Food intake before chemotherapy
Amount of sleep before chemotherapy
Severe emesis during pregnancy
Motion sickness
Treatment-specific factors
Drug
Dose
Infusion rate

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TABLE 13-4. FACTORS AFFECTING THE CONTROL AND INCIDENCE OF NAUSEA AND VOMITING AFTER CHEMOTHERAPY

ANTIEMETIC AGENTS

Most Active Agents

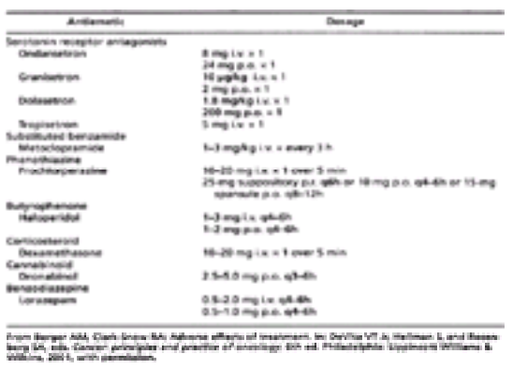
Antagonism of 5-HT3 is an important approach to controlling chemotherapy-induced emesis. Several agents are available that exert their efficacy in this manner. Metoclopramide, which was previously thought to block emesis by antagonism of a dopamine receptor ($D_2$3), probably works primarily via the 5-HT3 pathway at higher doses. This explains why higher doses of metoclopramide are more effective than lower doses (57). However, metoclopramide is not selective for the 5-HT3 pathway.

Several selective 5-HT3 antagonists are commercially available: dolasetron, granisetron, ondansetron, and tropisetron. Many multiple, randomized, well-controlled

studies have demonstrated that these agents have equivalent antiemetic activity and safety (58,59,60,61 and 62).

Nonetheless, some differences do exist among these agents. The differences are primarily in their structure and pharmacokinetic profile. However, to date none of these differences has been shown to be of clinical importance. All agents work by the identical mechanism: antagonism of the 5-HT3 receptor. All appear to accomplish this maximally, and differences among the relative potencies are unimportant at the recommended doses. There is no clear evidence that one of these agents will be effective when another is not. Half-lives in the serum vary from approximately 3–11 hours, but activity at the receptor appears to be similar in that single doses of all agents are equally effective. All agents have good bioavailability following oral administration; oral administration is as effective as is the intravenous route (63,64,65,66,67,68 and 69).

Controversy remains concerning the optimal dose of the serotonin antagonists. It appears that maximal benefit occurs once all relevant receptors are saturated. No matter what the emetic source, if the best results are to be achieved, an adequate dose should be given. Higher doses are not advantageous once all receptors have been saturated (70,71). In that these are very safe and well-tolerated agents, it has been difficult to define the best dose regimens. Different doses have been mandated in different countries. Several international consensus guidelines have been published, including those from the subcommittee for antiemetics of the Multinational Association of Supportive Care in Cancer, the American Association of Clinical Oncology, and the American Society of Health-System Pharmacists. As a general rule, the lowest adequately tested dose should be assumed to be the best dose in all settings (Table 13-5).



Antiemetic	Dosage
Serotonin receptor antagonists	
Ondansetron	8 mg i.v. × 1 24 mg p.o. × 1
Granisetron	10 μg/kg i.v. × 1 2 mg p.o. × 1
Dolasetron	1.8 mg/kg i.v. × 1 200 mg p.o. × 1
Tropisetron	5 mg i.v. × 1
Substituted benzamide	
Metoclopramide	1–3 mg/kg i.v. × every 3 h
Phenothiazine	
Prochlorperazine	10–20 mg i.v. × 1 over 5 min 25-mg suppository p.r. q8h or 10 mg p.o. q4-6h or 15-mg spansule p.o. q8-12h
Butyrophenone	
Haloperidol	1–3 mg i.v. q4-6h 1–2 mg p.o. q4-6h
Corticosteroid	
Dexamethasone	10–20 mg i.v. × 1 over 5 min
Cannabinoid	
Dronabinol	2.5–5.0 mg p.o. q3-6h
Benzodiazepine	
Lorazepam	0.5–2.0 mg i.v. q6-8h 0.5–1.0 mg p.o. q4-6h

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TABLE 13-5. DOSES, SCHEDULES, AND CLASSES OF COMMONLY ADMINISTERED ANTIEMETICS

Although some debate persists concerning the best dose of ondansetron, the majority of trials have indicated that the lower dose (8 mg) is as effective as the higher and far more expensive dose of 32 mg (72,73). The latter dose was superior in only one trial (74). The lower granisetron dose of 10 mg/kg is as effective in all circumstances as four times the dosage (75,76). The same dose recommendations continue for single-agent or combination use.

The side effect profile of the 5-HT3 antagonists provides a distinct advantage over other antiemetics. Central nervous system effects, extrapyramidal reactions, and sedation are not observed with serotonin antagonists. This is particularly beneficial in younger patients. Common side effects include mild headaches usually not requiring treatment, transient transaminase elevations, and constipation (77,78,79 and 80).

As indicated, the antiemetic activity of metoclopramide is likely as a serotonin antagonist, although it has substantial dopamine antagonist action as well. This latter mechanism explains the potential for extrapyramidal reactions. Studies have shown that higher doses are more effective (81,82). A dose of 3 mg/kg given every 2 hours for two doses in a combination regimen with corticosteroids has been found to be effective (83,84). To date, metoclopramide appears to be at least as effective as serotonin antagonists in preventing delayed emesis and is far less expensive (85,86 and 87).

Corticosteroids are valuable antiemetics. Dexamethasone is the best studied of these agents, is available in oral and parenteral preparations, and, in most countries, is very inexpensive. Although the optimal dose has not been established, it appears that a single 20-mg dose before chemotherapy administration is adequate, with no clear indication that either higher or lower doses is preferred (88). The other steroid that has been studied and that can be used is methylprednisolone. Caution must be used when treating diabetic patients or others with poor tolerance for corticosteroids. However, the short recommended course makes these agents safe and easy to use. In preventing delayed emesis, adequate doses of corticosteroids currently are viewed as the starting point of treatment, with some studies showing advantage for metoclopramide combined with steroids (89,90 and 91).

Efficacy for corticosteroids has been clearly outlined for cisplatin-containing regimens as well as other types of chemotherapy with lesser emetic potential (92,93,94,95,96,97 and 98). The addition of a corticosteroid to 5-HT3 antagonists significantly improves antiemetic efficacy with each of the agents. This is seen with cisplatin chemotherapy (99,100) as well as with anthracyclines, cyclophosphamide, and carboplatin (101). Double-blind studies have shown that efficacy is raised for 40% or 50% of patients having complete control with single agents, and 75% or 85% of patients with a combination of 5-HT3 antagonist plus a corticosteroid (102,103 and 104). This has led most investigators to advise that a corticosteroid should be added whenever the emetic source is thought to warrant a serotonin antagonist, unless a clearly documented reason for not using a corticosteroid in that patient has been demonstrated.

Antiemetics of Lower Activity

Phenothiazines, butyrophenones, and cannabinoids all have some degree of antiemetic efficacy. In general, this efficacy is substantially lower than that seen with the serotonin antagonists (including high-dose metoclopramide), and the side effects are greater (105). When given intravenously, phenothiazines appear to be more active than when given by other routes, but are associated with hypotension (especially orthostatic), which can be severe. Oral forms of all three of these agents exhibit only modest activity. Thus, these agents are not highly recommended.

Several cannabinoids have been tested in chemotherapy-induced emesis and are of both historic and lay press interest. Semisynthetic agents, such as nabilone and levonantradol; tetrahydrocannabinol, the active agent in marijuana; and inhaled marijuana, all appear to be of low and equal efficacy, with frequent autonomic side effects including dry mouth, hypotension, and dizziness (106,107). Dronabinol may be useful as an adjuvant to other antiemetics.

Antianxiety agents, such as the benzodiazepine lorazepam, have little efficacy as single agents in carefully conducted trials (108). However, they function well against anxiety in the emotionally charged atmosphere of receiving chemotherapy, although they add only a minor antiemetic effect to more active agents (109). They should be regarded as adjuncts to antiemetics and, in that role, can be useful for many patients. Recommended doses range from 0.5–1.5 mg. It is not clear that there is any advantage in giving these agents parenterally rather than orally. Additionally, these drugs may be useful when given to patients with anticipatory emesis, starting 1 or more days before the next chemotherapy dosing. Side effects mainly concern sedation, which can be marked in some patients, especially if the drug is given intravenously (Table 13-5).

DELAYED EMESIS

With the identification of useful antiemetics for the treatment of the acute emetic syndrome, it became apparent in patients receiving high total doses of cisplatin that, despite good control of emesis during the initial 24 hours after therapy, delayed emesis became an issue. To date, the pathophysiology of this especially difficult problem remains unclear. What is known, however, is that delayed emesis is a phenomenon observed in as many as 80% of patients, typically occurring 24–72 hours after high doses of cisplatin (>100 mg/m^2) have been administered (110). Delayed emesis may also be seen in a substantial number of patients who receive as little as 50 mg/m^2 cisplatin or a chemotherapy combination including cyclophosphamide and an anthracycline.

Initial studies revealed that delayed emesis could be controlled with a regimen of metoclopramide and dexamethasone (Table 13-6). Because of the possibility of extrapyramidal side effects, such as anxiety, akathisia, restlessness, torticollis, or oculogyric crisis, with metoclopramide, the patient should routinely be given a supply of diphenhydramine that should be taken at the first sign of an extrapyramidal symptom. In the younger patient, diphenhydramine should be given prophylactically.

Begin 16–24 h after cisplatin:
Days 1, 2: Metoclopramide, 0.5 mg/kg p.o. q.i.d.
plus
Dexamethasone, 8 mg p.o. b.i.d.
Days 3, 4: Dexamethasone, 4 mg p.o. b.i.d.
1. Diphenhydramine should be given at the first sign of extrapyramidal symptoms and prophylactically to the young patient.
2. Regimen to be given for cisplatin, >50 mg/m^2, or combination chemotherapy with an anthracycline and cyclophosphamide.
3. Oral 5-HT3 antagonists can be substituted for metoclopramide.

5-HT3, 5-hydroxytryptamine type 3.
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TABLE 13-6. RECOMMENDED REGIMEN FOR DELAYED EMESIS

Initial trials addressing the treatment of delayed emesis with the single-agent serotonin antagonist ondansetron were discouraging (111,112). Two randomized studies, one with ondansetron and one with granisetron, indicated efficacy of the serotonin antagonists for delayed emesis in patients receiving chemotherapy of intermediate emetogenicity (113,114).

As it is known from previous studies that a delayed antiemetic regimen with a substituted benzamide and dexamethasone controls the emesis, further research is needed to compare this standard regimen with a regimen of a serotonin antagonist and dexamethasone. One may need to differentiate between late-onset acute emesis (i.e., 18–48 hours after cyclophosphamide administration, for which oral granisetron and ondansetron have demonstrated benefit) versus true delayed emesis that is evident 2–7 days after cisplatin administration, for which the 5-HT3 antagonists may not have a large advantage over standard metoclopramide-based regimens. It is likely that the mechanism of action for delayed emesis is very different from that for acute chemotherapy-induced emesis, and perhaps serotonin is not involved at all. This should be addressed further in carefully controlled clinical trials, as the cost of the serotonin antagonists is far more than the cost of a substituted benzamide.

Another group of agents that have a potential role in the prevention of delayed nausea and vomiting are the NK1 antagonists. Substance P, which is found in the GI tract and the central nervous system and can produce vomiting when injected into ferrets, exerts its effects by binding to the neuroreceptor NK1. Hesketh et al. (115) reported on a randomized phase II study of the NK1-receptor antagonist CJ-11,974 in the control of cisplatin-induced emesis in 61 patients. This exploratory trial revealed that CJ-11,974 was superior to placebo in controlling delayed emesis and may provide additive benefit in acute emesis and nausea control when combined with a 5-HT3 antagonist and dexamethasone. In a multicenter, double-blind, placebo-controlled trial involving 159 patients who received a single dose of cisplatin, the NK1-receptor antagonist L-754,030 prevented delayed emesis and, in combination with granisetron plus dexamethasone, improved the prevention of acute emesis (116).

Other agents that may be of benefit in the treatment of delayed emesis include benzodiazepines, especially lorazepam and alprazolam; the H_2 blockers cimetidine and ranitidine; and omeprazole. Studies are currently under way on the use of cisapride, a potent gastric prokinetic agent that does not affect the D_2 receptors and, therefore, does not lead to adverse extrapyramidal effects.

ANTICIPATORY NAUSEA AND VOMITING

Anticipatory nausea and vomiting occurs approximately 24 hours before the patient begins chemotherapy. The symptoms may occur outside the hospital, in the clinic, when talking about chemotherapy, or when the patient perceives special tastes or odors.

Acute nausea and vomiting that occur with chemotherapy are thought to be secondary to the medication. The exact mechanism of posttreatment nausea and vomiting is unknown, though is most likely secondary to the chemotherapeutic agent itself. At times it may also involve a psychological mechanism. Anticipatory nausea and vomiting always involve a psychological mechanism in that episodes are triggered by events that are not secondary to the direct administration of the chemotherapeutic agent itself.

The prevalence of anticipatory nausea and vomiting is unclear, depending on the study cited and whether nausea and vomiting are analyzed separately. A review by Morrow and Dobkin (117) summarized 28 surveys that were carried out in North America since 1979. The prevalence of anticipatory nausea ranged anywhere from 14–63%, with a median of 33%. Many factors that appear to be associated with anticipatory nausea and vomiting have been studied (Table 13-7).

Severe postchemotherapy side effects
Schedule of chemotherapy
Numerous chemotherapy cycles
Chemotherapeutic agents with high emetogenic potential
Age
History of motion sickness
Anxiety
Depression
Taste and odors

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TABLE 13-7. FACTORS ASSOCIATED WITH AN INCREASED INCIDENCE OF ANTICIPATORY NAUSEA AND VOMITING

Numerous studies have revealed a relationship between severe postchemotherapy side effects and the development of anticipatory nausea and vomiting (118,119,120 and 121). The schedule of chemotherapy also appears to be related to anticipatory symptoms. Anticipatory symptoms are related to the emetogenicity of the chemotherapeutic agents in most studies (122,123 and 124). They also are related to the length of chemotherapy, in that patients who receive chemotherapy for longer periods have a higher incidence of anticipatory symptoms (125,126 and 127).

Motion sickness is a risk factor for the development of postchemotherapy nausea and vomiting (128). Studies by Morrow (129) of 608 patients and another study (130) of 355 patients found a significant relationship between motion sickness and anticipatory nausea and vomiting. In some studies, age appears to be related to anticipatory symptoms; anticipatory nausea and vomiting occur more often in patients younger than 45–50 years old (131,132,133 and 134). Possibly, age is related to anticipatory symptoms because younger patients receive stronger emetogenic chemotherapeutic agents, which leads to increased postchemotherapy nausea and vomiting and, therefore, increased anticipatory nausea and vomiting. Another proposed explanation is that younger patients have a higher level of anxiety while receiving chemotherapy, which may lead to increases in anticipatory symptoms. Both of these explanations are plausible, though current data do not support either (135).

Other factors reported to be related to anticipatory nausea and vomiting include expectations. Those patients with anticipatory symptoms report the expectation of developing nausea and vomiting after chemotherapy (136,137). Type and stage of cancer also are related to anticipatory nausea and vomiting (138,139). Anticipatory symptoms have been found to be correlated with a patient's previous response of nausea and vomiting to other situations (140). It has been noted that patients with anticipatory nausea and vomiting have higher levels of depression (141). A relationship between anxiety and anticipatory nausea and vomiting has also been noted, (142,143) although insufficient evidence is available to indicate how anxiety is related to anticipatory symptoms (144).

Several retrospective reviews have indicated that taste and odors are related to anticipatory nausea and vomiting (145,146,147,148 and 149). Though a prospective study did not reveal any relationship among taste, odors, and anticipatory nausea and vomiting, Bovbjerg et al. (150) reported a study in which they administered a beverage to patients before they received chemotherapy. The investigators found a clear relationship between anticipatory nausea and a special taste. Blasco (151) suggested that taste and odors may be involved not only in anticipatory nausea and vomiting but perhaps with postchemotherapy nausea and vomiting. Indeed, the role of taste and smell is largely unknown. However, it may be involved in a spectrum of GI complaints experienced by the patient with cancer. Studies by Bernstein

(152) suggest that a learned food aversion develops to specific tastes or food and occurs because of an association of the food with unpleasant symptoms, such as nausea and vomiting. This food aversion could partially explain the anorexia associated with cancer.

Antiemetics used in the treatment of acute nausea and vomiting induced by chemotherapy are ineffective in treating anticipatory nausea and vomiting. Many studies have indicated that behavioral techniques are effective in reducing anxiety as well as reducing or eliminating anticipatory nausea and vomiting. Effective behavioral techniques include progressive relaxation with guided imagery, systematic desensitization, hypnosis, and cognitive and intentional distraction (153,154,155 and 156).

In one report in the literature, a lemon solution given to a patient before the receipt of chemotherapy masked taste sensations so that the patient experienced decreased anticipatory nausea and vomiting (157). It has also been suggested that benzodiazepines, especially lorazepam, may be helpful in treating anticipatory nausea and vomiting. However, no formal studies have established lorazepam's effectiveness in this situation.

RADIATION-INDUCED NAUSEA AND VOMITING

The etiology of radiation-induced emesis, like chemotherapy-induced emesis, is not completely understood. However, it is clear that it is a complex, multifactorial event. The incidence, severity, and onset of radiation-induced emesis appear to be related to the size of the radiation field, the dose per fraction, and the site of irradiation. Radiation-induced emesis occurs acutely in more than 90% of patients who receive total body irradiation for bone marrow transplantation, within 30–60 minutes in more than 80% of patients who receive single high-dose or large-field hemi-body irradiation (>500 cGy), and within 2–3 weeks in approximately 50% of patients who receive conventional fractionated radiotherapy (200 cGy per fraction) to the upper abdomen (158). Radiation-induced emesis also occurs in those patients who receive radiosurgery to the area postrema in excess of 350–400 cGy in a single dose. The emesis usually occurs between 1 and 12 hours after the radiosurgery.

The exact mechanism of radiation-induced emesis is thought to be due to a peripheral mechanism in the GI tract or a central mechanism involving the CTZ. It has been proposed that several substances, including dopamine, catecholamines, and prostaglandins, are released and stimulate afferent visceral fibers, an action that initiates sensory signals to the CTZ. As a result of both preclinical and clinical studies with serotonin antagonists, it has been suggested that serotonin may be released from enterochromaffin cells of the GI tract and may mediate emesis via mechanisms involving the 5-HT3 receptors, visceral afferent fibers, and the CTZ. This mechanism is most likely involved when radiation is applied to the upper abdomen, hemibody, or total body. Radiosurgery to the area postrema most likely induces emesis from the release of serotonin in the CTZ (159).

Clinical studies in the past using metoclopramide, nabilone (cannabinoid derivative), and chlorpromazine in the treatment of radiation-induced emesis revealed a response of 50–58% (160,161). In a nonplacebo trial with domperidone, a dopamine antagonist, a response of 82% was reported (162). A nonrandomized trial comparing ondansetron with other antiemetics reported response rates of 100% for ondansetron versus 43% for other antiemetics and 19% for no antiemetic treatment for patients who received middle to upper hemibody irradiation (163). A randomized study by Priestman et al. (164) of patients who received radiotherapy to the abdomen, pelvis, and thoracolumbar spine reported response rates of 45% for metoclopramide versus 97% for ondansetron. A randomized, double-blind, placebo-controlled evaluation revealed oral ondansetron to be an effective therapy for the prevention of emesis induced by total body irradiation (165). Ondansetron has been reported to be effective in radiotherapy-induced emesis in children (166) as well as for patients who receive radiosurgery to the area postrema (167).

Data are available from two double-blind, randomized studies concerning oral granisetron, 2 mg once daily, in radiation-induced nausea and vomiting. In a study involving patients undergoing fractionated, upperabdominal radiation, patients who received oral granisetron had a significantly longer median time to first emesis than did those who received placebo (35 days vs. 9 days, respectively) and a longer median time to first nausea (11 days vs. 1 day, respectively) (168). In another study of patients undergoing total body irradiation, patients treated with oral granisetron had significantly greater complete control as compared to the historical control group over the entire 4-day treatment period (22% vs. 0%, respectively) (169). Fauser et al. (170) reported on the use of oral dolasetron for the control of emesis during total body irradiation and high-dose cyclophosphamide in patients undergoing allogeneic bone marrow transplantation.

NAUSEA AND VOMITING SECONDARY TO COMORBID CONDITIONS

A number of comorbid conditions also may lead to nausea and vomiting, even though the majority of patients with cancer develop nausea and vomiting as a result of chemotherapy or radiotherapy (Table 13-8). Because the mechanism of the nausea and vomiting secondary to comorbid conditions is not usually well understood, it is difficult to know which antiemetics may be helpful. A study by Bruera et al. (171) revealed that controlled-release metoclopramide is safe and effective in managing chronic nausea in patients with advanced cancer. Future studies are needed to determine the optimal doses of metoclopramide as well as other antiemetics that may be used in drug combinations (e.g., metoclopramide plus corticosteroids) for the nausea and vomiting secondary to the malignancy itself.

Central nervous system metastases
Peritonitis
Hepatic metastases
Uremia
Hypercalcemia
Volume depletion
Water intoxication
Adrenocortical insufficiency
Bowel obstruction
Deficiency of specific nutrients
Learned food aversion
Taste and smell alterations
Hunger satiety mechanisms
Narcotics
Psychological stress

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TABLE 13-8. COMORBID CONDITIONS THAT MAY LEAD TO NAUSEA AND VOMITING

COST AND BENEFIT OF ANTIEMETIC THERAPY

The important results of research that provide the medical community with additional chemotherapeutic choices and supportive care measures often translate into added health care costs for patients and families. With the increased use of expensive antiemetics and with managed care dictating the length of hospital stays, the emphasis is shifting to out-patient chemotherapy administration. The challenge for physicians becomes one of providing a treatment plan in which patients are offered state-of-the-art and cost-effective therapy. This can be accomplished by applying certain guidelines.

Specifically addressing 5-HT3 antagonist antiemetics and their associated cost, the choice among these agents should be made on the basis of acquisition costs and reimbursement differences. The 5-HT3 antagonists all have demonstrated equivalent efficacy and side effects. Therefore, once an effective dose has been established, there would be no advantage in exceeding this threshold dose. The 5-HT3 antagonist of lowest cost should be selected for administration. Single-dose regimens given in combination with a corticosteroid provide an effective and convenient alternative in antiemetic therapy. Regimens that take advantage of a completely oral route of administration are easy and convenient for patients and are likely to reduce nursing and pharmacy costs. However, prolonged use of oral serotonin antagonists should be avoided. Adherence by physicians and nurses to established doses and schedules of antiemetics and their appropriate use can be cost-effective measures for patients and institutions.

Nolte et al. (172) discussed guidelines developed by the Memorial Sloan-Kettering Cancer Center for the cost-effective use of 5-HT3 antagonists that resulted in substantial savings while treating more patients. The initial guidelines in 1993 were based on the premise that the dose of the intravenous 5-HT3 antagonist ondansetron, 8–32 mg, could be adjusted on the basis of emetogenic potential of the chemotherapeutic regimen schema proposed by Hesketh et al. (95). Cost savings were documented without affecting the quality of life. The guidelines were modified in 1994 to include granisetron, 10 mg/kg, for moderately or highly emetogenic chemotherapy. When oral granisetron tablets were approved in 1995 for the prevention of highly emetogenic chemotherapeutic regimens, the guidelines were further modified to incorporate the use of oral granisetron instead of intravenous 5-HT3 antagonists for moderately to highly emetogenic chemotherapy. Additional cost savings were realized while the quality of life of the patients was unaffected.

The use of an oral form of a 5-HT3 antagonist for highly emetogenic chemotherapy, when data from well-controlled trials demonstrate comparable efficacy to the intravenous formulation, appears to be cost-effective (173,174). One should take into consideration, when evaluating the results of these studies, whether a stringent efficacy end point was used. Some studies did not use “no nausea” as one of the criteria for a complete response. Because nausea was ranked as the most severe chemotherapy-related symptom according to a relatively recent survey, the effect of the agents on nausea should also be evaluated.

Economic considerations for the selection of antiemetic regimens should answer the following questions:

- Will the use of the regimens likely result in a reduced hospitalization?
- While receiving therapy, will patients be able to maintain their usual level of activity?
- Will nursing and pharmacy costs be reduced?
- Are there mandated restrictions on the use of an agent in hospital formularies and in clinical settings?
- Will the antiemetic regimen affect the patient's out-of-pocket expenses?

Extensive basic and clinical research has made it possible to control treatment-induced nausea and vomiting for most patients. With recognition and anticipation of nausea and vomiting, counseling of the patient and family, prophylactic intervention, flexibility in the therapeutic approach, and constant reassessment of the treatment plan, chemotherapy- and radiotherapy-induced nausea and vomiting can be managed effectively in 80–90% of patients. The progress made in the field of treatment-induced nausea and vomiting must be a paradigm for other symptoms faced by the cancer patient that lead to suffering and that affect the patient's quality of life.

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14

CHRONIC NAUSEA AND VOMITING

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Chronic nausea and vomiting are common and trouble-some problems in patients with advanced cancer. The reported prevalence of these symptoms varies, depending on patient characteristics and the assessment methods used for diagnosing chronic nausea and vomiting. Fainsinger et al. reported that 71 out of 100 patients in a palliative care unit required treatment for nausea in the last week of life (1). Data from the National Hospice Study (2) showed that nausea and vomiting developed in 62% of terminal cancer patients with prevalence rates of 40% in the last 6 weeks of life with women and younger patients reporting higher rates. In a prospective study of 1635 cancer patients referred to a pain clinic, Grond et al. (2a) reported a prevalence of 27% for nausea and 20% for vomiting.

There is no standardized definition for chronic nausea. For research purposes it is often defined as nausea lasting for more than 4 weeks. In a population of patients with advanced cancer and short life expectancy this definition excludes many patients. For our purposes the presence of nausea for more than 1 week, in the absence of a well-identified, self-limiting cause (e.g., chemotherapy or radiotherapy) will be used. Chronic nausea is often multifactorial and requires chronic treatment.

The purpose of this chapter is to review the pathophysiology, causes, assessment, and management of chronic nausea.

PATHOPHYSIOLOGY

Much of what we know about nausea and vomiting is based on research in patients receiving chemotherapy or radiotherapy and in patients with postoperative nausea and vomiting (3,4 and 5). Chronic nausea in cancer patients has not been well researched. In this patient population, research is much more difficult because many factors are present that may contribute to the mechanism of emesis. As a result, research on mechanisms and management of acute chemotherapy or radiotherapy-induced nausea in which there are fewer contributing factors may not apply to the population of patients with chronic symptoms.

The pathophysiology of chronic nausea is complex with multiple mechanisms of emesis. A number of neural pathways and neurotransmitters are likely to be involved in the production of chronic nausea and vomiting. In addition the importance of different mechanisms are likely to vary between individual patients.

Vomiting Center

The vomiting center is located in the nucleus of the tractus solitarius and the reticular formation in the medulla. This center receives input from a number of areas within the brain and the gastrointestinal (GI) tract. Histamine and acetylcholine appear to be the predominant neurotransmitters in the vomiting center. The vomiting center then produces the vomiting reflex. Afferent emetic pathways and neurotransmitters are summarized in Figure 14-1.

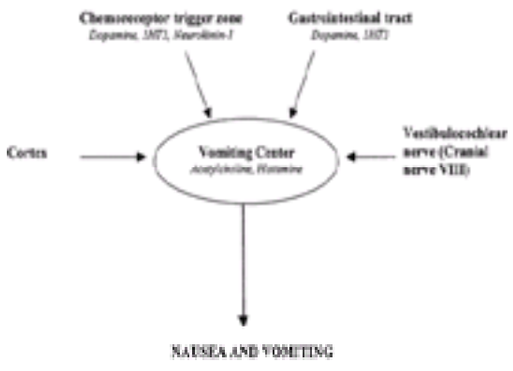

FIGURE 14-1. Afferent emetic pathways and neurotransmitters. 5HT3, 5-hydroxy-tryptamine type 3.

Chemoreceptor Trigger Zone

The chemoreceptor trigger zone (CTZ) is situated in the area postrema of the medulla. It samples cerebrospinal fluid and blood. Chemotherapeutic agents, metabolic products (e.g., uremia), opioids, and bacterial toxins produce nausea and vomiting by stimulating the CTZ. The CTZ initiates vomiting via the vomiting center. A neural pathway connects the two areas. The predominant neurotransmitters in this area are dopamine (D_2), serotonin (5-HT3), and neurokinin-1. The involvement of D_2 has been the basis for the use of drugs with antidopaminergic activity such as butyrophenones (haloperidol), phenothiazines, and metoclopramide. Serotonin antagonists and neurokinin-1-receptor antagonists are useful for the treatment of chemotherapy and radiotherapy-induced nausea.

Cortex

The cortex and other areas of the brain, such as the diencephalon and the limbic system, supply afferents to the vomiting center. Raised intracranial pressure, taste, smell, and anxiety can contribute to and stimulate vomiting. The brain cortex is also involved in emesis associated with thoughts, and visual or olfactory stimuli in patients receiving chemotherapy (6).

Vestibulocochlear Nerve

Motion can trigger nausea and vomiting. Opioids can alter the sensitivity of the vestibular center (7) resulting in nausea associated with movement. Motion stimulates receptors in the labyrinth. Impulses are then transmitted to the vestibular nucleus and onto the cerebellum, CTZ, and vomiting center. The frequency of nausea and vomiting is comparatively higher in ambulatory patients as compared to those confined to bed. The predominant neurotransmitters involved at this level are

acetylcholine and histamine. Anticholinergics and antihistamines are used for treatment.

Gastrointestinal Tract

The upper GI tract sends afferent impulses to the vomiting center via vagal and sympathetic stimulation. Stimulation of mechanoreceptors or chemoreceptors in the gut can cause nausea and vomiting. Gastrointestinal obstruction, gastric stasis, metastatic disease, bacterial toxins, drugs, chemotherapeutic agents, and irradiation can cause emesis in this way. In addition, stimulation of the glossopharyngeal or vagus nerves in the pharynx by sputum, candida, or mucosal lesions can cause nausea. Dopamine, acetylcholine, and 5-hydroxytryptamine are important neurotransmitters at the level of the upper GI tract.

CAUSES

Chronic nausea in advanced cancer patients is often multi-factorial. Figure 14-2 summarizes the common causes of chronic nausea in this patient population. In many patients the underlying cause or causes are difficult to determine.

FIGURE 14-2. Contributors to chronic nausea in patients with advanced cancer. NSAIDS, nonsteroidal antiinflammatory drugs.

Autonomic Failure

In some cancer patients chronic nausea is associated with the anorexia cachexia syndrome. In these patients autonomic failure is thought to be the most likely cause of chronic nausea (8). Autonomic failure causes gastroparesis, with resulting anorexia, nausea, and early satiety. In addition, other effects on the GI tract include diarrhea and constipation. Autonomic failure also has cardiovascular manifestations such as postural hypotension, syncope, and fixed heart rate.

Autonomic failure was originally described in patients with diabetes mellitus, neurological disorders, and chronic renal disease (8,9 and 10). More recently autonomic failure has been described in patients with advanced cancer. Kris et al. (11) reported delayed gastric emptying in 10 cancer patients who complained of chronic nausea and vomiting. Bruera et al. (12) looked at the incidence of cardiovascular autonomic insufficiency in 43 patients with advanced breast cancer and in 20 healthy controls matched for age and sex. Tests for autonomic failure were performed, and 52% of tests were abnormal in the patient group versus 7% in the control group. Autonomic failure in the cancer patient group was more common in those with poor performance status and malnutrition. In another study which included 5 patients with advanced cancer complaining of unexplained chronic nausea and anorexia, 16 out of 23 tests for autonomic function were abnormal, compared with none of 25 tests performed in five healthy adult controls (13). None of the five patients had clinical or laboratory evidence of disseminated disease to the abdomen or liver. All had normal endoscopy and barium meals with no evidence of mucosal injury. All five patients had severe gastroparesis (mean emptying time 192 ± 28 minutes) as compared to 5 controlled (mean emptying time 66 ± 5 minutes) when assessed with a gastric emptying scan. The differences between patients and controls were statistically significant; it was concluded that gastroparesis was the cause of chronic nausea and anorexia in these patients. There have been several other cases reported in the literature of autonomic dysfunction associated with lung and pancreatic cancers (14,15 and 16).

The cause of autonomic dysfunction in advanced cancer patients remains unclear and appears to be multifactorial. Malnutrition itself has been suggested as a cause of autonomic neuropathy (8). Jewish physicians in the Warsaw ghetto during World War II found that their starving patients were not able to increase their blood pressure with effort and had a constant tachycardia with no change upon standing up (17). Features of autonomic dysfunction have also been described in patients with anorexia nervosa. Studies on animals have suggested that fasting suppresses the activity of the sympathetic nervous system (18). There are isolated case reports suggesting autonomic dysfunction as a paraneoplastic manifestation of advanced cancer (19,20 and 21). Park et al. (20) reported a patient with bronchial carcinoma who showed postural hypotension and abnormal tests for autonomic dysfunction that disappeared after irradiation of the tumor. In a second report, a patient with small cell carcinoma of the lung developed intestinal obstruction and abnormal tests for autonomic dysfunction. An autopsy demonstrated degeneration of autonomic nerves without tumor involvement in the area. Antineuronal antibodies have been identified in patients with small cell lung carcinoma who demonstrated neurological signs consistent with autonomic neuropathy (22).

Another possible etiological factor in autonomic neuropathy in this patient population is direct tumor involvement (23). Cardiovascular autonomic neuropathy has been noted after the administration of chemotherapeutic agents such as vinca alkaloids (24). Drugs such as opioids, anticholinergics, antidepressants, and vasodilators may also have adverse effects on the autonomic nervous system. Many of these drugs are used in the management of cancer-related symptoms. Radiation damage to the autonomic ganglia is also a potential factor. Human immunodeficiency virus infection has also been noted to produce autonomic insufficiency (25).

Autonomic dysfunction is a frequent feature in patients with advanced cancer. It should be suspected in patients with unexplained tachycardia, poor performance status, chronic nausea, and malnutrition. Figure 14-3 summarizes the possible causes of autonomic dysfunction in advanced cancer patients.

FIGURE 14-3. Possible causes of autonomic dysfunction in advanced cancer patients.

Drugs

Opioids are one of the most common causes of chronic nausea in cancer patients. Opioid analgesia can cause nausea and vomiting in patients after initiation or increase in dose. This usually responds well to antiemetic medication and disappears spontaneously within the first 3 or 4 days of treatment (26,27). Some patients, particularly those receiving high doses of opioids, experience chronic and severe nausea (28).

Opioids cause chronic nausea by a number of mechanisms, including stimulation of the CTZ, gastroparesis, constipation, and by increasing sensitivity of the vestibular center (as discussed previously, see the section Vestibulocochlear Nerve) (7). The presence of opioid receptors in the CTZ in the area postrema is consistent with the observation of morphine and enkephalin-induced vomiting in the dog after local or systemic administration and the abolishment of this response after ablation of the

area postrema (29).

Chronic nausea has been associated with accumulation of active morphine metabolites such as morphine-6-glucuronide. Accumulation of morphine metabolites is more likely with higher doses of opioids but can occur even with lower doses, especially in patients with renal insufficiency (30).

Many other drugs can cause nausea. Nonsteroidal antiinflammatory drugs, antibiotics, and iron supplements can cause nausea irritation of the GI tract. Antibiotics may also cause nausea by a direct effect on the CTZ. Psychoactive medications including tricyclic antidepressants, selective 5-HT3 reuptake inhibitors, and phenothiazines can cause nausea.

Constipation

Constipation is common in patients with advanced cancer (31). Severe constipation can cause nausea and vomiting, abdominal pain, distention, urinary retention, and cognitive failure (32). There are many factors in advanced cancer patients that predispose to the development of constipation, including opioid analgesics, immobility, poor oral intake and dehydration, autonomic failure, and other medications. Constipation is often underdiagnosed in this patient population and should be suspected as a cause of nausea in all advanced cancer patients (33).

Bowel Obstruction

Bowel obstruction is a less common but important cause of nausea and vomiting. It has been reported to occur in 3% of all terminally ill cancer patients, and was found to be present in 15 of 100 consecutive patients admitted to a tertiary palliative care unit (34). Although acute complete bowel obstruction is easy to diagnose, the majority of advanced cancer patients tend to present with a less clear picture with a slow progression from partial to complete bowel obstruction. Some patients have only intermittent obstructive symptoms. These episodes of obstruction may be accompanied by nausea and vomiting.

ASSESSMENT

Because the causes of chronic nausea and vomiting are often multifactorial, the assessment in a given patient should be multidimensional, with awareness that these symptoms are dynamic processes and frequently change in intensity. There are a number of effective systems for assessing the intensity of nausea, such as visual analog scales, numerical scales, and verbal descriptors, but there is no “gold standard” for nausea assessment. As nausea is a subjective symptom, its expression varies from patient to patient and will depend on the individual patient's perception and other factors such as psychosocial issues. From a practical point of view this occasionally leads to a lack of correlation between the observed expression of nausea and the presumed pathophysiology of the underlying condition. It is also important to note that the term *nausea* may mean different things to different people and be used by some patients to describe other symptoms, including abdominal discomfort, pain, distention, or early satiety.

Once the intensity of nausea has been assessed, it is important to assess the symptom in the context of other symptoms such as pain, appetite, fatigue, depression, and anxiety. This multidimensional assessment allows formulation of a therapeutic strategy. An example of a validated multidimensional assessment tool is the Edmonton Symptom Assessment System (35,36) The system is based on visual analog scales that assess pain, nausea, anxiety, depression, appetite, shortness of breath, and sense of well being, among others. Tools such as this can be used to document the intensity of nausea initially, as a baseline assessment, and then on a regular basis, giving the examiner a sense of the therapeutic effect of the management. Such tools allow for a more reproducible assessment from the point of view of research and quality control.

A detailed history and physical examination is essential. It is important to clarify that the patient's expression of nausea does not describe a different symptom such as reflux. Intensity, frequency, exacerbating and relieving factors, onset, and duration of nausea should be documented. If there is coexistent vomiting, the nature of the vomiting should also be documented as the quantity of the vomitus can give a clue to the etiology. Large-volume emesis may indicate gastric outflow obstruction while small volume emesis may indicate gastric stasis. The extent to which the emesis interferes with oral intake should be noted, as large and frequent volume vomiting puts the patient at risk of rapid dehydration. A history of syncopal episodes or early satiety should alert the physician of the possibility of autonomic insufficiency.

The etiology of nausea may be related to the underlying cancer diagnosis. In patients with intraabdominal malignancies or metastases, bowel obstruction should be suspected. The stomach and duodenum can be compressed, causing the “squashed-stomach syndrome.” Symptoms and signs of raised intracranial pressure may indicate brain metastases.

A detailed medication history is essential. The use of drugs capable of causing nausea, such as opioids, anticholinergics, nonsteroidal antiinflammatories, and antibiotics, should be specifically noted. Other medical conditions, such as peptic ulcer disease and diabetes, should also be noted. Autonomic failure should be suspected in patients with diabetic neuropathy or chronic renal failure.

Constipation, as already discussed (see the section Constipation), is a common complication in advanced cancer patients and may cause or aggravate nausea. The frequency of bowel movements; feeling of abdominal distension; rectal soreness; oozing of stool; change in the amount of gases or stool passed recently; laxative use, type, and dose; and date of last bowel movement should be obtained. Unfortunately, clinical impression is likely to be quite unreliable and investigations, such as a plain abdominal x-ray, should be undertaken to help in the diagnosis (37). The use of a radiological constipation score may be necessary for adequate diagnosis in some patients, particularly those with cognitive failure. On a plain abdominal x-ray the abdomen is divided into four quadrants. Each quadrant is assessed for constipation: score, 0 = no stool; 1 = stool occupying <50% of the lumen; 2 = stool occupying >50% of the lumen; 3 = stool completely occupying the whole lumen of the colon. The total score of all quadrants is calculated and will range from 0–12. A score of 7/12 or greater is suggestive of severe constipation (33,37,38).

Physical examination may be helpful in identifying possible underlying causes. Table 14-1 summarizes possible findings on physical examination in patients with chronic nausea and vomiting.

General inspection
Cachexia or malnutrition; muscle wasting, skin fold thickness
Abdominal examination
Bowel obstruction; abdominal distention, increased bowel sounds
Abdominal masses or ascites
Constipation; abdominal fullness, including rectal examination
Neurological examination
Raised intracranial pressure; papilledema
Autonomic insufficiency; lying and standing blood pressure, absence of heart rate variation during Valsalva's maneuver

TABLE 14-1. POSSIBLE FINDINGS ON PHYSICAL EXAMINATION IN PATIENTS WITH CHRONIC NAUSEA AND VOMITING

Investigations to exclude renal impairment, hepatic failure, and other metabolic abnormalities such as hypercalcemia, hypokalemia, and hyponatremia should be undertaken. A computed tomography scan of the brain may be indicated where brain metastases are suspected. Abdominal x-rays may be useful in assessing nausea. A supine x-ray may indicate the presence of stool and fecal impaction. Erect or decubitus views may show air and fluid levels in the bowel, which is typical of bowel obstruction. Sophisticated investigations, such as gastric emptying scans, are probably not justified for the majority of patients.

MANAGEMENT

Appropriate management of chronic nausea and vomiting depends on a detailed assessment. The formulation of a management plan and decisions regarding the type of antiemetic medication to use depend on the postulated underlying cause or causes of the nausea. General support measures should be instituted. In addition, specific and symptomatic treatment should be undertaken as appropriate.

General Support Measures

General measures should address maintenance of good oral hygiene (poor oral hygiene can contribute to nausea), the creation of a comfortable environment for the patient, regular baths to prevent unpleasant body odors, and attention to diet. Small volumes of food at regular intervals should be considered for patients with early satiety associated with nausea.

Specific Treatment

In patients where an underlying cause or causes have been identified, there should be an attempt to correct these. Metabolic abnormalities should be corrected if this is possible. In situations where opioid toxicity is suspected, a change of opioids using equianalgesic doses can be expected to improve symptoms of nausea while maintaining pain control (39). Unnecessary medications should be discontinued. Aggressive bowel care, including cleansing enemas and regular laxatives, should be instituted when constipation or stool impaction is suspected. In some cases, such as in patients with brain metastases, symptom control may be attempted with radiation therapy or corticosteroids. If peptic ulcer disease is suspected, appropriate treatment should be instituted.

Symptomatic Treatment

Pharmacological Interventions

Many drugs with antiemetic properties are available for the treatment of chronic nausea and vomiting. Table 14-2 summarizes current and possible future agents.

Agent	Effects
Dopamine antagonists central action (e.g., metoclopramide, butyrophenone, phenothiazine)	Block dopamine at chemoreceptor trigger zone.
Dopamine antagonists peripheral action (e.g., metoclopramide, domperidone)	Promotility effects on gastrointestinal tract.
Anticholinergics (e.g., cyclizine, promethazine, dimenhydrinate)	Effects on vomiting center and vestibular apparatus.
Corticosteroids (e.g., dexamethasone)	Reduce raised intracranial pressure, other antiemetic effects not well understood. Also improve sensation of well-being and appetite.
5-HT3 antagonists (e.g., ondansetron, granisetron)	Block 5-HT3 (serotonin), useful in chemotherapy-induced and postoperative vomiting.
Progestational agents (e.g., megestrol acetate)	Unknown. Improve appetite, caloric intake, and nutritional variables in cancer cachexia.
Thalidomide	Centrally acting antiemetic effect. Other effects on improving appetite and sensation of well-being.
Cannabinoids	Central effects.
Neurokinin-1 antagonists (not yet licensed)	Central effects, antagonize substance P.
Octreotide	Reduced gastrointestinal secretions in patients with inoperable bowel obstruction.
Anticholinergic agents, e.g., hyoscine butylbromide	Reduced gastrointestinal secretions in patients with inoperable bowel obstruction.

5-HT3, 5-hydroxytryptamine type 3.

TABLE 14-2. ESTABLISHED AND EMERGING AGENTS FOR THE TREATMENT OF NAUSEA

Prokinetic Drugs

The initial pharmacological management of chronic nausea and vomiting in most patients should involve prokinetic drugs to normalize upper GI motility (40,41,42 and 43). Metoclopramide and domperidone are examples of prokinetic drugs. Metoclopramide has been established as an effective drug for treating delayed gastric emptying in patients who do not have cancer in a number of controlled clinical trials (43). Metoclopramide has also been demonstrated to be effective in reversing tumor-associated gastroparesis (11,42) and nausea associated with advanced cancer (28,40,44). Metoclopramide antagonizes D_2 both centrally in the CTZ and peripherally in the GI tract. In addition, it exhibits weak antagonism at the 5-HT3 receptor. In our experience metoclopramide is the drug of first choice for patients with chronic nausea (28). High doses of metoclopramide (1–2 mg/kg given up to 5 times in 24 hours) may produce 5-HT3 receptor blockade, which may in turn contribute to its antiemetic activity. However these high doses are frequently impractical. One problem with the administration of metoclopramide is its short elimination half-life, which necessitates frequent administration to provide optimal relief of nausea. Clinical trials support the view that sustained metoclopramide concentrations are required to suppress nausea and vomiting and possibly other GI symptoms associated with advanced cancer (28,45,46). As a result some patients require frequent administration or continuous infusions for optimal results (47). In a recent study, 26 cancer patients with a greater than 1-month history of dyspepsia were randomized to receive either controlled-release metoclopramide 40 mg 12 hourly or placebo for 4 days (40). Patients were then crossed over to the alternative treatment for another 4 days. On the last day of each treatment phase, nausea was significantly lower in the controlled-release metoclopramide group compared to placebo. Controlled-release metoclopramide was well tolerated and adverse events did not differ between treatments and placebo groups. In another study immediate-release metoclopramide 20 mg 6 hourly was compared to controlled-release metoclopramide 40 mg 12 hourly in patients with advanced cancer and chronic nausea. Nausea scores by day 3 of treatment were significantly lower for patients who received controlled release as compared to immediate-release metoclopramide (44). Metoclopramide occasionally causes acute dystonic reactions. These are more common in younger patients, especially in young men. Domperidone is another drug with antidopaminergic activity. However it does not readily cross the blood–brain barrier and acts primarily on the GI tract. Hence, it is less likely to cause central effects such as extrapyramidal reactions and sedation.

A standard therapeutic ladder for the management of chronic nausea in cancer patients based on metoclopramide has been developed. Table 14-3 summarizes this regimen. A retrospective assessment of this regimen in 98 terminally ill patients with nausea in a palliative care unit found that the majority of patients without bowel obstruction achieved excellent control of nausea using this regimen. Twenty-five patients (25%) required other antiemetics, 18 because of GI obstruction, three due to extrapyramidal side effects, and four for other reasons. These data suggest that nausea can be controlled in the majority of patients in this population.

Step 1	Metoclopramide, 10 mg p.o./s.c. q4h + 10 mg p.o./s.c. for rescue
	Poor response after at least 2 d of treatment (consistent complaint of nausea and >2 extra doses of metoclopramide per day), go to step 2; occasionally patients with severe emesis go to step 3
	Side effects or contraindication (bowel obstruction), go to step 4
Step 2	Metoclopramide (same dose as step 1) + dexamethasone, 10 mg p.o./s.c. b.i.d.
	Poor response after at least 2 d, go to step 3
	Side effects or contraindication, go to step 4
Step 3	Continuous subcutaneous infusion of metoclopramide (60–120 mg/d) + dexamethasone, 10 mg p.o./s.c. b.i.d.
	Poor response, go to step 4
Step 4	Other antiemetics (e.g., haloperidol, dimenhydrinate)

TABLE 14-3. A METOCLOPRAMIDE-BASED REGIMEN FOR TREATMENT OF CHRONIC NAUSEA

Other Centrally Acting Dopamine Antagonists

Phenothiazines (e.g., chlorpromazine) and butyrophenones (e.g., haloperidol) are effective antiemetics. They are D_2 antagonists and act centrally at the CTZ. They do not increase GI motility and are thus useful in patients with complete bowel obstruction (48). Phenothiazines are more sedating than butyrophenones and this effect limits their use in this patient population.

Antihistamines

Antihistamines (e.g., cyclizine, promethazine, and dimenhydrinate) are useful antiemetics particularly if a vestibular component to the nausea is suspected.

Corticosteroids

Corticosteroids have powerful nonspecific antiemetic effects that are not well understood. They can decrease peritumoral edema, thus reducing intracranial pressure, a known cause of nausea. Corticosteroids are beneficial in combination with other antiemetic agents such as 5-HT3 antagonists or metoclopramide in the prevention and management of acute chemotherapy-induced emesis (49,50). Corticosteroids are also useful in the management of other symptoms that may coexist with nausea in advanced cancer patients such as pain, anorexia, and asthenia (51,52 and 53).

Serotonin Antagonists

5-HT3 antagonists are widely used and researched for the prevention and management of acute chemotherapy-induced nausea and vomiting (49,54). There are case reports of nausea refractory to other treatments being effectively treated by 5-HT3 antagonists (55,56). However, no clinical trials have been published on the use of 5-HT3 antagonists in the management of chronic nausea.

Progestational Agents

Trials involving progestational agents in the treatment of hormone-responsive tumors found significant body weight gain with or without tumor response (57,58). This prompted studies of these drugs for the treatment of cancer cachexia. Megestrol acetate has been the most widely studied progestational agent in patients with advanced cancer. Several randomized controlled trials have shown that megestrol acetate can improve appetite, caloric intake, and nutritional variables in patients with cancer cachexia (59,60,61,62,63 and 64). Simons et al. (65) found improved appetite and possible reduction in nausea and vomiting in patients with advanced-stage, nonhormone-sensitive cancer treated with megestrol acetate (65). Loprinzi et al. (60), in a randomized, placebo-controlled trial of megestrol acetate involving 133 patients, reported a significantly reduced incidence of nausea and vomiting in patients receiving megestrol acetate. Reduced nausea has also been reported in other studies of megestrol acetate in cancer cachexia (61,62). Further research is needed to assess the potential role of progestational agents in the treatment of patients with chronic nausea.

Thalidomide

This drug was initially used during the 1950s as a mild anxiolytic, hypnotic, and antiemetic. Its antiemetic effects resulted in its use in the treatment of hyperemesis gravidarum (66,67), and was found to be effective in the symptomatic therapy of nausea and vomiting caused by malignant, nongastric neoplasms or by the administration of mechlorethamine (68). It was removed from the market after it was found to cause severe teratogenesis when administered to pregnant women. Its antiemetic effect is thought to be a central effect. In recent years there has been renewed interest in thalidomide, particularly for use in cancer patients. In addition to central antiemetic and sedative effects, thalidomide has immunomodulatory, antipyretic, anticachectic, and possible antiangiogenic, antidiaphoretic, and analgesic actions (69). This spectrum of potential effects makes it an interesting drug from a palliative care perspective. Bruera et al. (70) found that the administration of thalidomide 100 mg at night in 37 evaluable patients with advanced cancer and cachexia led to significant improvement in appetite, nausea, and sensation of well being. Further research is needed to evaluate the effects of thalidomide on chronic nausea.

Cannabinoids

Several studies have demonstrated the efficacy of dronabinol as an antiemetic agent for the treatment of chemotherapy-induced nausea and vomiting (71,72,73 and 74). A randomized controlled trial in 139 patients with acquired immunodeficiency syndrome cachexia comparing oral dronabinol 2.5 mg twice daily and placebo showed significant improvement in nausea, appetite, and mood but no body weight gain in those patients taking the drug (75). Side effects, such as somnolence, confusion, and perceptual disturbance, are common (73). The effects of cannabinoids in advanced cancer patients with chronic nausea have not been characterized. In this patient population who frequently have borderline cognitive impairment and are often receiving other medications, such as opioids and other psychoactive drugs, the incidence of side effects is likely to limit their use.

Neurokinin-1-Receptor Antagonists

The application of substance P to the nucleus tractus solitarii induces vomiting (76). The action of substance P is mediated through the neurokinin-1 receptor. Neurokinin-1-receptor antagonists have been found to inhibit cisplatin-induced emesis in animals (77,78). In a recent multicenter double-blind, placebo-controlled trial, 159 patients were randomized to one of three groups prior to receiving their first dose of cisplatin. All patients received granisetron and dexamethasone prior to cisplatin. Group 1 received an oral neurokinin-1-receptor antagonists (L-754,030) prior to cisplatin and on days 2–5 after cisplatin, group 2 received L-754,030 prior to cisplatin and placebo in days 2–5 afterwards, and group 3 received placebo before and on days 2–5 after cisplatin therapy. The neurokinin-1-receptor antagonist was found to prevent delayed emesis after treatment with cisplatin. It was also found to improve the prevention of acute cisplatin-induced emesis when combined with granisetron and dexamethasone as compared to placebo combined with granisetron and dexamethasone (79). No significant differences were observed in the incidence of adverse effects between the three groups. Hesketh et al. reported similar findings with another neurokinin-1-receptor antagonist (CJ-11,974) in patients receiving cisplatin. Improved control of delayed emesis and a possible additive benefit for prevention of acute emesis when combined with a 5-HT3 antagonist and dexamethasone were observed (80). Neurokinin-1-receptor antagonists have also been reported to be more effective than placebo in the treatment of established postoperative nausea and vomiting (81). The potential role of neurokinin-1-receptor antagonists in the treatment of chronic nausea and vomiting of cancer is currently unknown.

Octreotide and Anticholinergic Drugs

In patients with inoperable bowel obstruction, reduction of secretions has been achieved using anticholinergic agents (e.g., hyoscine butylbromide) (82) and octreotide (a somatostatin analogue) (83). Two recent randomized controlled trials have compared anticholinergic agents and octreotide. Mercadante et al. (84), in a study involving 18 patients, found that octreotide treatment produced a significantly reduced number of daily episodes of vomiting and intensity of nausea compared with hyoscine butylbromide. Lower levels of hydration were associated with nausea in both groups. Ripamonti et al. (85) looked at 17 patients who presented with inoperable bowel obstruction and a decompressive nasogastric tube. Patients were randomized to receive either octreotide 0.3 mg or scopolamine butylbromide 60 mg daily for 3 days by subcutaneous infusion. It was possible to remove the nasogastric tube in 13 of the 17 patients. Octreotide significantly reduced the amount of GI secretions at days 2 and 3 as compared to scopolamine butylbromide. Patients who received less parenteral hydration had significantly more nausea and drowsiness. The authors concluded that octreotide should be considered the first-choice drug when a rapid reduction in GI secretions is desired and that parenteral hydration over 500 ml/day may reduce nausea and drowsiness. Further studies are needed to identify the role that hydration plays in the etiology of nausea in this clinical situation.

Surgical Intervention

In patients with nausea and vomiting caused by intestinal obstruction, surgical procedures should be considered. Percutaneous gastrostomy for gastric outlet obstruction can greatly improve symptoms in some patients (34,86). Laparotomy for GI obstruction due to tumor or adhesions can abolish symptoms and improve life expectancy and quality. Surgery should be considered if a bypass procedure or excision of the obstructing lesion is possible and the patient's general physical condition suggests a life expectancy long enough to result in a likely benefit from surgery.

CONCLUSION

Chronic nausea and vomiting are common and distressing symptoms in patients with terminal cancer. These symptoms are likely to be due to several factors, including autonomic failure, opioid analgesics, metabolic abnormalities, constipation, and cachexia. Promotility agents (sometimes in combination with corticosteroids) are in most cases the drug of choice for management of chronic nausea and vomiting. Pharmacological agents, such as progestational drugs and thalidomide, need further evaluation of their potential beneficial effects in patients with chronic nausea. Despite significant ongoing research into acute chemotherapy-induced and postoperative emesis, research is lacking in chronic nausea. Drugs that have been found to be effective in acute vomiting, such as 5-HT3 and neurokinin-1-receptor antagonists, require further evaluation in advanced cancer patients with chronic nausea.

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15

DIARRHEA, MALABSORPTION, AND CONSTIPATION

SEBASTIANO MERCADANTE

DIARRHEA

Diarrhea is commonly defined as an abnormal looseness of the stools (increased liquidity or decreased consistency). It occurs when the intestine does not complete absorption of electrolytes and water from luminal content. Although a practical definition of diarrhea is lacking, diarrhea is commonly diagnosed when an abnormal increase in daily stool weight, water content, and frequency, whether or not accompanied by urgency, perianal discomfort, or incontinence, is present (1).

Diarrhea is a common complication in the cancer population, occurring in 5–10% of patients with advanced disease (2,3 and 4). The consequences of diarrhea can be troublesome, and include loss of water, electrolytes, albumin, and failure to reach nutritional goals, declining immune function, and the risk of bedsores or systemic infection. Diarrhea also brings additional work for the nursing staff or family who have to prevent maceration and bedsores. Moreover, losses of comfort and dignity have to be considered.

Diarrhea principally induces dehydration. Several symptoms depend on dehydration, such as asthenia, anorexia, weight loss, and drowsiness, which limit the quality of life. Furthermore, it determines abnormal metabolic compartments influencing drug pharmacokinetics, blood renal flow, and acid-base balance, as well as hypokalemia and acidosis from massive potassium and bicarbonate loss (5).

Mechanisms

The presence in the lumen of unusual amounts of poorly absorbable, osmotically active solutes; intestinal ion secretion or inhibition of normal active ion absorption with or without exudation of mucus, blood, and protein from sites of inflammation; and deranged intestinal mobility constitute the principal mechanisms to produce diarrhea.

Osmotic Diarrhea

The ingestion of a poorly absorbable solute modifies the osmolarity of the luminal content and induces osmotic diarrhea (Table 15-1). The proximal small bowel is highly permeable to water; sodium and water influx across the duodenum rapidly adjust the osmolarity of luminal fluid toward that of plasma, secreting water even after the osmolarity values between luminal contents and plasma are similar. On the contrary, the mucosa of the ileum and colon has a low permeability to sodium and solutes. However, there is an efficient active ion transport mechanism that allows the reabsorption of electrolytes and water even against electrochemical gradients (1).

Carbohydrate malabsorption
Excessive ingestion of poorly absorbed carbohydrate
Magnesium-induced diarrhea
Laxatives containing poorly absorbable anions

TABLE 15-1. CAUSES OF OSMOTIC DIARRHEA

Carbohydrates and proteins are fermented by colonic bacteria and salvaged as short-chain fatty acids and gases. Anaerobic colonic flora are necessary for the fermentation of fiber into short-chain fatty acids and constitute the bulk of fecal mass. In the perioperative period, cancer patients may receive massive antibiotic therapy, able to suppress normal colonic metabolism, thus resulting in diarrhea (6). When large amounts of lactulose, an unabsorbable sugar in the small intestine, are ingested, the protective role of colonic bacteria may be exhausted, resulting in severe diarrhea. Fecal volume in carbohydrate-induced diarrhea is proportional to the osmotic force of the malabsorbed saccharide (7). Carbohydrate malabsorption may induce osmotic diarrhea. It is characterized by a low stool pH, due to the presence of short-chain fatty acids, a high content of carbohydrates, high stool osmolarity, and flatulence. In osmotic diarrhea caused by ingestion of magnesium, sulfate, and poorly absorbed salts, there will be a normal pH. Osmotic diarrhea commonly subsides as the patient fasts or stops ingesting poorly absorbable solutes laxatives. It is characterized by an osmotic gap in stool analysis, equivalent to the concentration of the osmotically active agents in fecal fluid that are causing diarrhea (1).

Secretory Diarrhea

An abnormal ion transport in intestinal epithelial cells, with a reduction in absorptive function or increase in secretion of epithelial cells, is observed in secretory diarrhea. Secretory diarrhea is rarely present as the sole mechanism and is often associated with other mechanisms (6).

Different from osmotic diarrhea, the anionic gap is small, eating does not markedly increase stool volume, and diarrhea usually persists during periods of fasting. Secretory diarrhea can result from bacterial toxins, or the presence of intraluminal secretagogues (such as bile acids or laxatives), circulating secretagogues (such as various hormones, drugs, and poisons), and other medical problems that compromise regulation of intestinal function, or reduce absorptive surface area (by disease or resection) (8). Secretagogues are substances stimulating the intestine to secrete fluid acting mostly via the enteric nervous system (9). Endocrine tumors may cause diarrhea via the release of secretagogue transmitters (10). Diarrhea is a common manifestation of a carcinoid syndrome, occurring in approximately 70% of patients. Intestinal secretion seems to be mediated by serotonin and substance P. In the Zollinger-Ellison syndrome, secretory diarrhea is the consequence of gastric hypersecretion caused by a high concentration of circulating gastrin, overwhelming the intestinal absorptive capacity. Severe diarrhea with hypergastrinemia due to lansoprazole rather than gastrinoma has been reported (11). In a medullary carcinoma of the thyroid, circulating calcitonin is the major mediator of intestinal secretion (1).

Malabsorption is often associated with diarrhea. Malabsorption due to bile salts rendered insoluble by the low intraluminal pH is often associated with this. Ileal resection or a postvagotomy state may result in watery diarrhea from the secretory effect of malabsorbed bile acids on colonic mucosa. Malabsorption due to lymphatic obstruction and fibrosis induced by the tumor may contribute to diarrhea (12) (see Malabsorption).

The cancer treatment–related diarrhea caused by acute graft-versus-host disease (GVHD) and chemotherapeutic agents (13), particularly fluoropyrimidines, paclitaxel, and irinotecan, significantly affects morbidity and mortality. Diarrhea is a significant consequence of colorectal chemotherapy, with the majority of patients experiencing grades 3 or 4 diarrhea and 56% of all patients also modifying their chemotherapy regimen (14). These agents cause acute damage to the intestinal mucosa, necrosis, and extensive inflammation of the bowel wall. Mucosal and submucosal factors, produced directly or indirectly by the inflamed intestine, stimulate secretion of intestinal fluid and electrolytes. Similar anatomical changes have been observed in patients with GVHD diarrhea, as well as with radiation enteritis (13).

Extensive necrosis of epithelial cells increases the risk of superinfection by opportunistic pathogens such as *Clostridium difficile*, *Clostridium perfringens*, *Bacillus cereus*, *Giardia lamblia*, *Cryptosporidium*, *Salmonella*, *Shigella*, *Campylobacter*, and *Rotavirus*. This risk is highest in patients who may be neutropenic or immunosuppressed. Bacterial enterotoxins or other infective agents induce secretion probably by a local nervous reflex mediated by enteroendo-crine cells or inflammation (1). The incidence of *C. difficile*-induced diarrhea is very high: 2.2% in patients receiving standard-dose regimens and 20% in patients receiving high-dose regimens (15,16 and 17).

Cancer patients who are immunocompromised or recently underwent surgery often are administered a long-term antibiotic therapy for resistant infections. These aggressive treatments, including ampicillin, clindamycin, or cephalosporins, may result in a disruption of the normal flora and overgrowth of pathogens. *C. difficile*, an anaerobic organism producing an enteric toxin, is the common cause of pseudomembranous enterocolitis, which presents itself as a severe microbial diarrhea (18). Other infectious agents include *C. perfringens*, *Staphylococcus aureus*, *Klebsiella oxytoca*, candida species, and salmonella species (17).

Some drugs, such as diuretics, caffeine, theophylline, antacids, antibiotics, and poorly absorbable laxative agents and osmotically active solutes, often chronically administered in a palliative care setting, may produce secretory diarrhea, mostly causing a reflex nervous secretion or directly activating secretory cellular mechanism (6).

Deranged Motility

When other measurable mechanisms are excluded, motility derangements should be suspected to be the cause of diarrhea. Even in the presence of a normal absorptive function of epithelial cells, defective motility may reduce the contact time between luminal contents and epithelial cells. This commonly occurs in cancer patients with postsurgical disorders, such as postgastrectomy dumping syndrome, postvagotomy, ileocecal valve resection, or neoplastic and chronic diseases, such as malignant carcinoid syndrome, medullary carcinoma of thyroid, and diabetes (19). The diabetic population can be affected by diarrhea as a result of severe neuropathy. The mechanism by which diabetic neuropathy causes dismobility is attributed to a sympathetic denervation of the bowel with a prevalence of cholinergic innervation (20). An iatrogenic autonomic neuropathy due to celiac plexus block, a procedure used to abolish visceral abdominal cancer pain, has been described. The sympathetic denervation of the bowel may leave a cholinergic innervation unopposed, leading to an increase in intestinal motility and diarrhea. This phenomenon is generally self-limiting (21).

An abnormal reduced mobility due to spinal cord damages may favor a bacterial overgrowth, which induces a deconjugation of bile acids in the small bowel and thereby causes diarrhea and steatorrhea. Diarrhea secondary to dysmotility disorders commonly subsides after a 1–2-day fast, determining a small stool volume and an osmolality in the range of 250–300 mOsm.

Assessment

The patient should be questioned in detail about dietary habits of food intolerance. The use of any prescription or antibiotics in the preceding few weeks should be noted. The assessment of concomitant diseases or previous surgical intervention can provide important clues about the etiology. Frequency, amounts, and consistency of the stools should be carefully obtained. When the stools are consistently large, light in color, watery or greasy, free of blood, or contain undigested food particles, the underlying disorder is likely to be in the small bowel or the proximal colon. But small stool diarrhea in which frequent but small quantities of feces, dark in color, often containing mucus or blood, pass in spite of a sense of urgency, is associated with a disorder of the left colon or rectum (1). These two patterns of diarrhea may occur simultaneously because of widespread inflammation. Fecal incontinence, change in stool caliber, rectal bleeding, and small, frequent, but otherwise normal stools have to be distinguished. Passage of nonbloody diarrheal fluid, pus, or exudates indicates an inflammatory or infectious disease. Diarrhea associated with excessive flatus and mushy stools suggests carbohydrate malabsorption. Intermittent diarrhea and constipation are frequent in diabetic neuropathy, as well as in irritable bowel syndrome or subobstructive disorders. Complaints of nocturnal diarrhea and fecal soiling are frequently reported by patients with autonomic neuropathy or anal sphincter dysfunction. From the clinical point of view, the suspicion of a partial obstruction should be raised in the case of sudden diarrhea after a period of constipation. Fecal impaction may cause apparent diarrhea because only liquids pass a partial obstruction. Therefore, alternating diarrhea and constipation suggests fixed colonic obstruction. Abdominal x-ray will help the diagnosis. The presence of a mass suggests a possible malignancy, especially if associated to hepatosplenomegaly (6). Rectal examination and abdominal palpation should be performed to look for fecal masses and to exclude fecal impaction and intestinal obstruction. Rectal involvement is probable in the presence of little or no stool in spite of a sense of rectal urgency, commonly named *tenesmus*.

Physical examination, laboratory findings, and signs and symptoms may reveal important clues to the cause of diarrhea, including abdominal mass, perianal fistula or abscess, signs of anemia, fever, postural hypotension, lymphadenopathy, neuropathy, hepatosplenomegaly, ascites, gaseous abdominal distention or lymphadenopathy, reduced anal sphincter tone, a rectal mass or impaction, fever, and deterioration of nutritional status. Symptoms of dumping syndrome after gastric surgery, such as early nausea, abdominal distention, weakness, and diarrhea after a meal followed by hypoglycemia, sweating, dizziness, and tachycardia, are typical. Secretory diarrhea combined with upper gastrointestinal symptoms caused by refractory peptic ulcer disease is suggestive of gastrin-secreting tumor. High circulating serotonin levels in carcinoid syndrome cause other effects besides diarrhea, including hypotension, sweating, flushing, palpitation, and wheeziness (1,6). Peripheral or autonomic neuropathy confirms the possible concomitant visceral neuropathy secondary to these diseases. The association of heat intolerance, palpitations, and weight loss suggests possible hyperthyroidism. Chronic bowel ischemia should be considered in the oldest patients with the clinical feature of diffuse atherosclerotic disease. Of course, the site of neoplasm and metastases is of paramount importance. The location of the tumor will be verified by computed tomography, magnetic resonance imaging scan, angiography, or laparoscopy. Intestinal dysmotility or bacterial overgrowth due to diabetes, neoplastic conditions, or postoperative conditions may be associated with diarrhea (6).

If feasible, collected diarrhea stool specimen should be submitted for qualitative study. Positive finding in either the stool guaiac or leukocyte test gives suspect to an exudative mechanism, as does happen in radiation colitis, colonic neoplasm, or infective diarrhea. Stool cultures for bacterial, fungal, and viral pathogens, as well as formal evaluation of the gastrointestinal tract should complete the initial assessment (1,13).

Watery diarrhea is generally sustained by infective agents and efforts should be made for this purpose. Gram's stain of stool can diagnose the presence of *Staphylococcus*, *Campylobacter*, or *Candida* infection. Multiple stool cultures should be obtained from patients with secretory diarrhea to rule out microorganisms producing enterotoxins, which stimulate intestinal secretion. The presence of a microorganism in the stools is diagnostic (1). Chemotherapy-induced diarrhea typically occurs 2–14 days after therapy. Incidence of delayed diarrhea has been reported as high as 80% with irinotecan (22). Number of stools per day, need for parenteral support or intensive care, nocturnal stools, and episodes of incontinence are common toxicity criteria to evaluate treatment-induced diarrhea.

Radiation colitis is probable in patients who have received pelvic radiation for malignancies of the urogenital tract and of the prostate (1). The need for primary prevention is becoming urgent because evidence is emerging that suggests the problem has an increasing frequency. The early acute syndrome, manifesting itself with diarrhea, is usually self-limiting and probably consequent to inflammatory reactions.

Osmotic diarrhea is associated with a reduction of stool content in sodium and potassium that produces an anion gap of more than 50 mmol/l, while secretory diarrhea, due, for example, to endocrine tumors presenting an active secretion of salts and water, is characterized by lower values (less than 50 mmol/l). Moreover, while osmotic diarrhea typically stops or reduces after fasting or stopping the drug previously used, secretory diarrhea persists in spite of fasting (1,6).

Treatment

Considering the different mechanisms involved in determining diarrhea in cancer patients, there are no broadly accepted treatment protocols. Current medication should be revised, considering the use of laxatives, antacids, theophylline preparations, central nervous system drugs, antiarrhythmics, and antibiotics.

Dietary advices are difficult to follow in cancer patients. A gluten-free diet can reduce abdominal cramping and bowel movement frequency in the presence of intestinal fermentation with bowel distention. Binders of osmotically active substances (kaolin-pectin) give a thicker consistency to loose stools, producing a viscous, colloidal, absorbent solution, but their antidiarrheal effectiveness is disputable. Apples without the peel are particularly rich in pectin. Other dietary advices include avoiding cold

meals, milk, vegetables rich in fibers, fatty meat and fish, coffee, and alcohol. Oral hydration solutions containing glucose, electrolytes, and water are the simplest and most common treatments. Complex carbohydrate rather than monomeric forms improves water and electrolyte absorption (22). However, clinical signs of dehydration, such as orthostatic hypotension, decreased skin turgor, and a dry mouth, suggest the need of intensive hydration by intravenous route, especially in patients suffering from nausea and vomiting in which oral therapy is ineffective (6).

Drugs for Radiation Enteritis

Cholestyramine has been favorably used in radiation-induced diarrhea. However, real progress will come from the prevention of radiation enteritis rather than from changes in its management. Aspirin has been reported effective in postradiotherapy diarrhea (23). The effects are attributed to the reduction of prostaglandin synthesis responsible for water and electrolyte secretion. Sucralfate has been shown to mitigate diarrhea after pelvic radiation therapy. However, recent controlled studies were not able to demonstrate significant benefits. Moreover, some gastrointestinal symptoms, such as fecal incontinence, need for protective clothing, and severity of nausea, were worse among patients taking sucralfate (24).

Silicate smectite has proven a promising drug in the prophylaxis of radiotherapy-induced diarrhea. Patients with a low, irradiated, small bowel volume show the greater benefit, with a delay in the development of diarrhea after irradiation of pelvis and the abdomen (25).

Steroids

Steroids may exert a positive effect on secretory diarrhea, probably due to their antiinflammatory activity. Cortico-steroids can be useful in reducing edema in intestinal pseudo-obstruction or in radiation-induced enteritis. Moreover, steroids can reduce hormone secretion in endocrine tumors, reduce the release and the effect of the inflammation mediators, and promote salts and water absorption acting on sodium pump and sodium-hydrogen exchange (1). They are also included in the pharmacological approach to GVHD-induced diarrhea (13). Budesonide, a topical active steroid, demonstrated a substantial activity in irinotecan and 5-fluorouracil–induced diarrhea after failure of loperamide treatment (26).

Antibiotics

Antibiotics, such as norfloxacin and amoxicillin-clavulanic acid, are effective in the treatment of bacterial overgrowth– related diarrhea (27). On the other hand, antibiotic-associated diarrhea (pseudomembranous enterocolitis) requires the discontinuation of antibiotics and the starting of either metronidazole or vancomycin (28). It often subsides spontaneously after stopping the antibiotics. Bismuth subsalicylate in doses of 30–60 ml every 30 minutes for eight doses may bring mild symptomatic relief in patients with acute infectious diarrhea with an unknown effect (29). Probiotic bacteria (i.e., live bacteria that survive passage through the gastrointestinal tract) may have beneficial effects on the host. In a recent review, probiotic bacteria consistently shortened the diarrheal phase of rotavirus infection, although the evidence for other viral or bacterial infections was less strong (30).

Other Drugs

Racecadotril, an enkephalinase inhibitor with antisecretory and antidiarrheal actions, has been found to be an effective and safe treatment for watery diarrhea, allowing for a reduction of oral rehydration, although no experience has been reported in cancer patients yet (31).

Clonidine, an a-2 agonist, has been reported useful in controlling diarrhea in diabetic patients or in patients with chronic idiopathic secretory diarrhea who present a reduced intestinal sympathetic tone and denervation supersensitivity. The increase of salts and water absorption is probably due to an interaction with enterocyte receptors and the suppression of secretory transmitter release. However, hypotension and sedation may limit the usefulness of clonidine in dehydrated or advanced cancer patients (5).

Opioids

Opioids are commonly used for their antidiarrheal properties. Opioid receptors are represented at different sites, including smooth muscle, myenteric plexus, spinal cord, and brain. Their activation influences intestinal motility and, as a consequence, secretion. Although a central action cannot be excluded, only peripheral mechanisms have been confirmed. Antidiarrheal effects can be obtained by both oral and parenteral opioids. Opioids increase ileocecal tone, decrease small intestine and colon peristalsis (increasing electrolyte and water absorption), impair the defecation reflex by inhibiting anorectal sphincteric relaxation, and diminish anorectal sensitivity to distention.

The contact time between intestinal mucosa and luminal contents is enhanced by the reduction of colonic propulsive activity, resulting in a greater fluid absorption (19).

Opioid-like agents, including codeine, morphine, diphenoxylate, and loperamide, represent the best known drugs for the symptomatic treatment of diarrhea. Loperamide is able to reduce ileal calcium fluxes, with an activity independent from the opioid effect, and does not cross the blood– brain barrier, whereas diphenoxylate rarely reaches significant opioid effects at a clinical dosage. Loperamide induces a long-lasting stimulation of colonic motility associated with a disorganization of cyclic motor activity, enhancing nonpropulsive contraction in the small intestine and the colon. The effects on the colon are probably mediated by a local mechanism. Loperamide shows the highest antidiarrheal/analgesic ratio among the opioidlike agents and proved to be the drug of choice due to its few adverse effects. The standard dose of loperamide is 4 mg followed by 2 mg after every unformed stool. The dosage should be titrated against the effect and higher doses, 2 mg every 2 hours have been recommended (up to 12 mg/day or more) in conjunction with chemotherapeutic agents associated with a high incidence of diarrhea (32). Loperamide-simethicone combination was significantly more effective than the drugs taken alone in the treatment of acute diarrhea with gas-related abdominal discomfort (33). However, the risk of producing paralytic ileus in the presence of continuous secretion should be considered as a life-threatening complication. Opioids may also cause a paradoxical diarrhea secondary to fecal impaction (19).

Octreotide

Refractory diarrhea that does not respond to specific therapy may present a challenging and serious clinical problem. Octreotide, an analogue of somatostatin with a more favorable pharmacokinetic profile, exerts a wide range of physiological effects on the gastrointestinal tract (5,34,35). Data from several clinical trials suggest that this antisecretory agent may be useful in the symptomatic treatment of diarrhea refractory to other medications. The mechanism by which octreotide produces these beneficial effects is probably multifactorial. It suppresses the secretion of many of the gut peptides implicated in the control of secretory and motor activity. Furthermore, it inhibits exocrine secretions from the stomach, pancreas, and small intestine, also facilitating water and electrolyte absorption (21). Octreotide has been found to control diarrhea due to carcinoid tumors, vipoma, gastrinoma, small cell lung cancer, as well as acquired immunodeficiency syndrome–related diarrhea (21,36), although hormonal responses to the somatostatin analogue do not always parallel clinical responses, probably because of the effects of cosecreted peptides. A dose-response effect of octreotide has been demonstrated (38,39). Octreotide seems to be an effective agent in the management of chemotherapy-related diarrhea and refractory GVHD-associated diarrhea (35,37,38,39,40,41,42 and 43). Finally, octreotide has been proven effective in the treatment of diarrhea induced by celiac plexus block, as well as diabetic diarrhea (21). Doses of 0.3–1.2 mg a day subcutaneously are commonly effective.

Long-acting, biodegradable, microsphere formulation of octreotide for monthly subcutaneous administration has been developed and could be evaluated for the prophylaxis of diarrhea in patients with a history of chemotherapy-induced diarrhea and in patients requiring high-dose chemotherapy or undergoing high-dose chemotherapy before autologous bone marrow cell transplantation.

MALABSORPTION

The term *malabsorption* refers to an ineffective absorption of breakdown products in the small intestine. Malabsorption may occur either because a disorder interferes with the digestion of food or directly with the absorption of nutrients. Different sequential stages of digestion and absorption may be affected in the cancer patient resulting in malabsorption. The series of events include the reduction of particle size, the solubilization of hydrophobic lipids and the enzymatic digestion of nutrients to small fragments, the absorption of the products of digestion across the intestinal cells, and the transport via lymphatics. The digestive and absorptive processes are inextricably linked.

Digestion

Pancreatic secretion of lipase, amylase, and proteases breaks down fat to monoglycerides and fatty acids, carbohydrates to mono- and disaccharides, and proteins to peptides and amino acids. Several processes have been recognized to facilitate the absorption of fat from the aqueous luminal environment, including emulsification, enzymatic hydrolysis, dispersion, diffusion, absorption, and intracellular metabolism. Triglycerides are emulsified together with phospholipids, bile salts, and mono- and diglycerides and dispersed into a variety of phases and particles. Lipid digestion by lingual lipase, active at low pH, begins in the mouth and in the stomach, promoting

emulsion stability and facilitating the action of pancreatic lipases. Gastric and pyloric motility further promote emulsification of lipids. This effect is amplified by bile salts and biliary phospholipids, which also influence the absorption of cholesterol and sterol vitamins. Lipolysis to fatty acids and monoglycerides is mediated by pancreatic lipases (6).

Protein digestion begins in the stomach. Acid denaturation prepares proteolysis. Proteolytic enzymes, endopeptidases activated by an acid environment, cleave the internal bonds of large proteins to form nonabsorbable peptides. Pancreatic peptidases convert proteins and polypeptides into amino acids and oligopeptides. After hormonal or neural stimulation, proenzymes are released by the pancreas. Enteropeptidases and trypsin activate a cascade of events that promote the activation of chymotrypsin, elastase, and carboxypeptidase A and B in the duodenum (44).

Pathophysiology

The hydrolysis of fat, protein, and carbohydrate by pancreatic enzymes, as well as solubilization of fat by bile salts, may be altered by several conditions (1,45). In such conditions, the intraluminal environment of the proximal small intestine resembles that of the colon. In pancreatic carcinoma or following pancreatic resection, decreased pancreatic enzymes and bicarbonate release may limit the digestion of fat and protein, leading to pancreatic insufficiency (46). These disorders may also be associated with malabsorption of fat-soluble vitamins. The Zollinger-Ellison syndrome is characterized by an extreme acid hypersecretion, causing a low luminal pH, inactivating pancreatic enzymes with consequent fat malabsorption. A decrease in intraluminal bile salts due to disruption of the enterohepatic circulation is also seen in patients with Zollinger-Ellison syndrome. Biliary tract obstruction, terminal ileal resection, or cholestatic liver disease result in decreased bile salts formation or delivery to the duodenum (47). Many postsurgical disorders have been associated with a marked proliferation of intraluminal microorganisms, including an afferent loop of a Billroth II partial gastrectomy, a surgical blind loop with end-to-side anastomosis, or a recirculating loop with side-to-side anastomosis. With limited small bowel resections, malabsorbed bile acids pass into the colon, decreasing water and electrolyte absorption, resulting in diarrhea. In massive small bowel resection, steatorrhea is caused by a diminished bile acid pool from increased intestinal bile salts loss, together with a loss of the absorptive intestinal surface and bacterial overgrowth (48).

Bacterial overgrowth competes with the human host for nutrients causing catabolism of carbohydrates by gram-negative aerobes, deconjugation of bile salts by anaerobes, and the binding of cobalamin by anaerobes. Causes of bacterial overgrowth include obstruction or strictures, autonomic neuropathy, and resection of the ileocecal valve. All of these conditions cause malabsorption by changing the intraluminal environment of the proximal small intestine so that it more closely resembles the colon (44).

Absorption

Absorption is the passage of these products of digestion from the lumen through the enterocyte to appear in the lymphatics or the portal vein. Several processes are involved in absorption. Active transport requires energy to move nutrients against a gradient, whereas passive diffusion allows nutrients to pass according to gradient differentials. Facilitated diffusion is an intermediate mechanism, similar to passive diffusion, but carrier-mediated and subject to competitive inhibition. Endocytosis is a process in which parts of a cell membrane engulf nutrients.

Carbohydrate absorption occurs as monosaccharides, predominantly in the proximal small intestine, although not all dietary carbohydrate is absorbed. The simple diffusion of monosaccharides across membranes is slow but important in the presence of high luminal concentrations of glucose. Specific active transport systems, especially via sodium-coupled transporters, mediate efficient transport of these substances when luminal concentrations of glucose are low. Monosaccharides may also enter enterocytes by facilitated diffusion. The uptake of lactose is limited by lactase activity. Xylose is not digested and has a low affinity for carriers. Some carbohydrates reach the colon and are fermented by bacteria into short-chain fatty acids with production of gases such as hydrogen and methane. Short-chain fatty acids are subsequently absorbed by colonic epithelial cells.

Fat products rapidly diffuse passively into enterocytes, with the rate of transfer depending on the chain length. Fatty acids and monoglycerides are metabolized into triglycerides and assembled with phospholipids and cholesterol esters into chylomicrons. Short- and medium-chain fatty acids have a less complex absorptive mechanism. They may be absorbed intact by passive diffusion or completely hydrolyzed, but they are not reesterified inside the enterocytes. Lipid absorption is highly efficient; only small amounts of lipids enter the colon. These may be absorbed by the colonic mucosa or undergo bacterial metabolism.

Bile salts are synthesized from cholesterol in the liver, conjugated with amino acids, secreted into the bile, and recycled back to the liver via the portal system. Minimal daily losses are balanced by hepatic synthesis. Passive diffusion and active transport are involved in bile salt transport in the small intestine to limit fecal loss. A certain amount of bile salt in the colonic lumen is essential for normal colonic function. In the colon, bile salts are not absorbed but they stimulate colonic motility and secretion of sodium chloride and water. In contrast, bile salt deficiency may cause constipation (6).

Amino acids are absorbed by enterocytes, oligopeptides are digested by the enterocyte, brush border by oligo- or dipeptidases. A specific transport mechanism exists for the intracellular transport of amino acids and dipeptides. Protein absorption is efficient and mainly occurs in the jejunum and ileum (44,45).

Pathophysiology

Abnormalities of the small intestinal mucosa or impairment of epithelial cell transport may be seen in radiation enteritis. The pathological changes from radiation enteritis occur in three phases. During and immediately after irradiation, abnormal epithelial cell proliferation, maturation, and inflammatory cell infiltration occur. An acute vasculopathy coincides in time with the period of maximal epithelial cell damage. Vascular changes may be progressive, even after the resolution of the acute epithelial changes. Subsequently, the intestinal mucosa regenerates to a variable extent depending on the vascular damage. Extensive fibrosis, strictures, and fistulae, with disruption of the mucosal surface, may develop resulting in a chronically inflamed bowel with impairment of mucosal function. Moreover, severe adhesions may develop between loops of intestine leading to the formation of fistulous tracts between adjacent bowel loops. Extensive mucosal damage, lymphatic obstruction, and bacterial overgrowth are the principal mechanisms of radiation-induced malabsorption (49).

A large surgical resection of the small intestine also reduces the epithelial surface area available for absorption. The extent and specific level of resection are predictive of severe malabsorption and short-bowel syndrome. Most patients with short-bowel syndrome either have a high jejunostomy with a residual jejunal length less than 100 cm or a jejunocolic anastomosis (45,48). The recovery from massive small bowel resection depends on the adaptive response of the remaining mucosa (50). Resection of more than 50% of the small intestine still results in significant malabsorption. The inclusion of the distal two thirds of the ileum and ileocecal sphincter in the resected section increases the risk of malabsorption. Preservation of the ileocecal sphincter is important because it may prevent small bowel contamination from colonic flora and may increase the transit time of the intraluminal content.

After intestinal resections, increased amount of bile salts reach the colon, promoting water and electrolyte secretion, unless liver production may compensate the losses, as it happens in limited resections. The consequent lack of solubilization of intraluminal fat will worsen the effects of bile salts on the colon mucosa. Enterostomy or intestinal fistulae may also result in a reduced absorption due to the loss of intestinal surface area. A vagotomy may increase the colonic content of bile acids due to an accelerated transit time. A diabetic neuropathy may result in intestinal dysmotility and bacterial overgrowth, and as a consequence, in malabsorption (6).

Lymphatic transport of chylomicrons and proteins is limited by lymphatic obstruction, leading to dilatation and potential rupture of intestinal lymphatic vessels, causing intestinal leakage of proteins, chylomicrons, and small lymphocytes. Localized ileal tumors, diffuse intestinal lymphomas, metastatic carcinoma, and metastatic carcinoid disease may all lead to lymphatic obstruction, fat malabsorption, and protein-losing enteropathy (6).

Assessment

Patients with malabsorption usually lose weight. If fats are not properly absorbed, the stools are light-colored, soft, bulky, and foul smelling. Such stool is called steatorrhea. Documentation of steatorrhea is the cornerstone of the diagnostic evaluation. Malabsorption can cause deficiencies of all nutrients or of proteins, fats, vitamins, or minerals selectively. Certain physical signs are frequently associated with specific deficiency states secondary to malabsorption, such as glossitis in folate or vitamin B_{12} deficiency, hyperkeratosis, ecchymoses, and hematuria due to fat-soluble vitamin deficiency (vitamins A and K). Anemia (chronic blood loss or malabsorption of iron, folate, or vitamin B_{12}), leukocytosis with eosinophilia, low serum levels or albumin, iron, cholesterol, and an extension of the prothrombin time are the most common laboratory findings in malabsorption (6,44). Impaired absorption of calcium and magnesium may induce weakness, paresthesias, and tetany. Osteopenia and bone pain, spontaneous fractures, and vertebral collapse may develop from vitamin D and calcium deficiency. Peripheral neuropathy may occur after gastric resection due to vitamin B_{12} deficiency. Weakness, severe weight loss, and fatigue result from caloric deprivation. In pancreatic carcinoma, floating, bulky, and malodorous stools and increased gas production are often associated with anorexia. Steatorrhea, peripheral lymphocytopenia, hypoalbuminemia, chylous ascites, and peripheral edema are the hallmarks of abnormalities of lymphatic transport. Symptoms of dumping syndrome after gastrectomy include early nausea, abdominal distention, weakness, and diarrhea after a meal, followed by hypoglycemia, sweating, dizziness, and tachycardia.

Other symptoms depend on the disorder that is causing the malabsorption. For example, an obstructed bile duct may cause jaundice; poor blood supply to the intestine

may cause abdominal pain.

Malabsorption is suspected when a person loses weight and has diarrhea and nutritional deficiencies despite eating well, although weight loss alone can have other causes in cancer patients.

Reviewing current drugs is important in the diagnostic evaluation. Colchicine, neomycin, and clindamycin are the most common drugs causing malabsorption, although the pathophysiologic mechanisms are unknown. Dietary phosphate absorption may be limited by use of aluminum-containing antacids, resulting in hypophosphatemia and hypercalciuria.

Laboratory tests can help confirm the diagnosis. Tests that directly measure fat in stool samples are the most reliable ones for diagnosing malabsorption of fat. Other laboratory tests can detect malabsorption of other specific substances, such as lactose or vitamin B_{12}. Undigested food fragments may mean that food passes through the intestine too rapidly.Such fragments also can indicate an anatomical abnormal intestinal pathway, such as a direct connection between the stomach and the large intestine that bypasses the small intestine. Small intestinal barium x-rays may define anatomical abnormalities after massive resection. Biochemical examination of the fecal material may give information about the origin of a fistula (pancreatic or enteric). Liver function tests and imaging of the liver or biliary tract may demonstrate parenchymal liver disease as a cause of decreased production of bile salts or a biliary tract obstruction.

Treatment

After assessing the causes of malabsorption, therapy should be directed to correct the deficiencies, including enzyme replacement, bicarbonate supplements, vitamins, calcium, magnesium, and iron. Pancreatic enzyme replacement along with a low-fat, high-protein diet is indicated in the case of malabsorption due to pancreatic insufficiency. The effectiveness of enzyme replacements is variable and, in part, depends on a high enough gastric pH to prevent their degradation in the stomach (51). Large doses of pancreatic extract are required with each meal. Sodium and bicarbonate, or anti-H_2 inhibitors and hydrogen pump inhibitors, are mainly added to raise the duodenal pH.

Fat intake should be strictly limited, especially in short-bowel syndrome. Medium-chain triglycerides may be substituted for long-chain triglycerides to improve fat absorption after a small intestinal resection, and they are useful in the presence of lymphatic obstruction because they do not require intestinal lymphatic transport (52).

For patients with prominent dumping, dietary modification comprising frequent small, dry meals that are high in protein and low in carbohydrates, along with ingestion of substances that prolong the absorption of carbohydrates, such as pectin, may be useful (5).

An aggressive approach should be reserved in the presence of severe malnutrition and dehydration, especially after surgery. Parenteral nutrition is strongly indicated in the immediate postoperative period after massive intestinal resection. The duration of parenteral nutrition is inversely proportional to the length of the remaining intestine. The weaning to oral nutrition depends on several variables including the preoperative nutritional state, the absorptive deficit, and the tolerance to oral intake. Oral feeding should be started as soon as possible, as adaptation of the remaining bowel to resection is facilitated by the early introduction of oral or enteral nutrients (53). Moreover, intraluminal nutrients stimulate trophic gastrointestinal hormones regulating mucosal repair. H_2-blocking agents may also favorably influence the rate of adaptation of remaining intestine after massive resection, possibly by a mucosal trophic effect improving nutrient absorption. Nutrients requiring minimal digestion for absorption should be chosen, such as commercial preparations containing simple sugars, amino acids, or oligopeptides, as well as medium-chain triglycerides. An excessive osmolar load should be avoided to prevent the occurrence of diarrhea. More complex food should be added gradually.

Vitamin B_{12} replacement is necessary after terminal ileal resection. H_2 blockers are used to treat the transient acid hypersecretion after extensive bowel resection or the acid hypersecretion state in patients with gastrinoma (Zollinger-Ellison syndrome) (44). Omeprazole inhibits the hydrogen-potassium proton pump and produces a greater antisecretory effect than that achieved by H_2-antagonist drugs alone. The use of cholestyramine should be carefully examined. It may be indicated in limited intestinal resections because it binds bile salts and prevents their irritant effects on the colon. However, in short-bowel syndrome after massive intestinal resection, it may reduce the bile salt pool, thus increasing fat malabsorption. The dose suggested is 4 g three times daily before meals. Aluminum hydroxide exerts similar effects.

Antibiotic-associated malnutrition requires discontinuation of any implicated antimicrobial agents. However, if there is stasis with bacterial overgrowth caused by impaired motility or stricture, such as in radiation enteritis or blind loop syndrome, broad-spectrum antibiotics should be administered. A 10-day course of a cephalosporin and metronidazole seems to be effective in suppressing the flora and correcting malabsorption. However, cyclic therapy may be needed (44).

In patients affected by malabsorption due to short-bowel syndrome, it is useful to reduce the intestinal output or the transit time. Codeine and loperamide can delay the transit time or reduce secretions (6). Somatostatin and, more recently, its derivative octreotide, have been used because of their ability to reduce gastric, pancreatic, and biliary secretions, as well as intestinal transit time. Octreotide possesses the same spectrum of effects as somatostatin but is more potent, has a long half-life, has less influence on insulin secretion than somatostatin, and, above all, can be administered by the subcutaneous route (21). Dosages from 0.2–0.6 mg daily have been advocated. It may reduce or shorten the use of parenteral administration in several postoperative conditions, such as enterocutaneous or pancreatic fistulae. Its use has been favorably reported in terminally ill patients (5). Reversal of a short segment of the bowel or construction of a recirculating loop have been advocated in patients with life-threatening malabsorption and uncontrolled weight loss. However, such operations may lead to stasis and bacterial overgrowth, and they may further compromise intestinal absorption. More often than not, these procedures fail to provide significant benefit (6).

CONSTIPATION

Constipation is extremely common in patients with cancer, especially in the advanced status of disease. Approximately 45% of hospice patients complain of constipation at admission (3,4,54). Constipation is defined in different ways as straining, hard stools, the desire but inability to defecate, infrequent stools, and abdominal discomfort. While stool weight and consistency are unreliable parameters because of the wide range in normal subjects (6), stool frequency is typically the most common parameter considered. A frequency of at least three bowel movements per week is viewed as an objective indicator of normality. In addition to causing discomfort, constipation affects daily living, nutritional intake, and socialization, thus compromising quality of life. Untreated constipation may progress to obstipation, which may potentially lead to life-threatening complications associated with bowel obstruction (55).

Pathophysiology

In cancer patients, constipation may be secondary to systemic diseases or those solely afflicting the gastrointestinal tract. It may be directly due to a cancer or to secondary effects of the cancer. Many drugs used by cancer patients may induce constipation. In Table 15-2, the most frequent causes of constipation are listed.

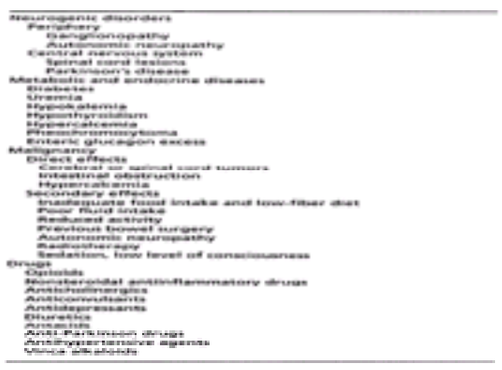

TABLE 15-2. CAUSES OF CONSTIPATION IN CANCER PATIENTS

Constipation is frequently noted by patients with various neurological disorders. A visceral neuropathy seems to be present in the majority of patients with severe slow-transit constipation. Disturbance in the extrinsic nerve supply to the colon has been found in these patients, along with a lack of inhibitory innervation of colonic circular muscle, and a diminished release of acetylcholine. Patients with advanced cancer frequently complain of gastrointestinal symptoms, including anorexia, chronic nausea, and early satiety—a symptom complex often associated with physical signs of an autonomic neuropathy. Autonomic neuropathy may also be manifested as severe constipation, including postural hypotension and resting tachycardia. It is a multifactorial syndrome, and malnutrition, decreased activity, diabetes, and drugs,

such as vinca alkaloids, opioids, and tricyclic antidepressants, are all possible causative factors (6).

Diabetic dysmotility has traditionally been thought to reflect a generalized autonomic neuropathy. However, secretions of gastrointestinal hormones may also be important. Decreased amounts of substance P in the rectal mucosa of constipated diabetic patients has been thought to contribute to the pathogenesis of diabetic constipation (56).

Peripheral neuropathy is a common complication of cancer chemotherapy. Patients receiving a high cumulative dose of vincristine or cisplatin seem to be at a significantly elevated risk for the development of long-term side effects (57). These drugs have been shown to cause symptoms of autonomic polyneuropathy with constipation, bladder atony, and hypotension. Whereas many reports describe acute neurological side effects during therapy, little is known about persistent and late damage to the peripheral nervous system. The long-term neurological side effects in patients with curable malignancies, such as Hodgkin's disease and testicular cancer, may be particularly troublesome.

Long-term denervation abolishes the normal pelvic floor muscle activity. This neurological impairment may be produced by nerve damage not only following chemotherapy, but also as a consequence of radiotherapy, pelvic surgery, compression, or invasion by neoplastic growth or during prolonged chronic opioid therapy. A loss of the normal rectal muscle tone is also a consequence of prolonged immobility often seen in debilitated cancer patients. Rectal sensation may be reduced and the rectal capacity to distention increased after vincristine treatment or as a consequence of neoplastic involvement of the pelvic sacral nerves (6). The rectosigmoid junction is a key area in the mechanism of constipation. Rectal outlet obstruction and failure of the puborectalis and anal sphincter muscles to relax are frequent findings in patients with neurological diseases with intractable constipation. Several mechanisms of constipation by outlet obstruction are possible, including a hyperactive rectosigmoid junction, an increased storage capacity of the rectum, spasticity, and hypertonicity of the anal canal with incoordination of the reflex between rectum and anus. Anismus is a spastic pelvic floor syndrome, recently termed *rectosphincteric dyssynergia*, for its similarity with vesicourethral dyssynergia. Similar extrinsic innervation of the bladder and the rectum has been observed, explaining why patients with severe slow-transit constipation often complain of urological symptoms.

The integrity of the spinal cord neurons is essential to maintain normal defecation. After spinal cord lesions above the lumbosacral area, incontinence is controlled but defecation is impaired. This is due to interruption of the cortical pathways, demonstrating the importance of supraspinal control of distal colonic function and defecation. Moreover, colonic response to a meal is reduced. However, appropriate stimuli may be sufficient to result in evacuation. In patients with damage to the cauda equina, transit time is prolonged and the rectoanal inhibitory reflex is weaker, offering little protection against fecal incontinence (19).

In cancer patients with Parkinson's disease, constipation is probably caused by the degeneration of the autonomic nervous system, particularly the myenteric plexus (58). Psychiatric and neurological diseases are frequently associated with colonic dysmotility (19).

Ogilvie's syndrome describes a variety of states with a similar clinical picture due to intrinsic defects in the intestinal smooth muscle, with a massive colonic dilatation in the absence of an obstruction or inflammatory process (59). Also termed as *pseudo-obstruction*, this syndrome can be categorized into those with myopathic and those with neuropathic features. Several conditions involving the intestinal smooth muscle are associated with colonic pseudo-obstruction, including endocrine and metabolic disorders, neurological diseases, nonoperative trauma, surgery, nonintestinal inflammatory processes, infections, malignancy, radiation therapy, drugs, and cardiovascular and respiratory diseases. Extensive damage to the submucosal and myenteric nerve plexus associated with lymphoid infiltrate has been observed as a specific disorder, different from other processes that produce intestinal pseudo-obstruction (60).

A large variety of metabolic disorders predispose to constipation. Of particular relevance to cancer patients are dehydration, hypercalcemia, hypokalemia, and uremia. Chronic dehydration can also result in dry stools that are difficult to expel. Many drugs induce constipation.

Many drugs with anticholinergic actions, antiemetics, and diuretics induce constipation. Patients treated with carbamazepine may develop severe constipation that is not dose related but is refractory to the concomitant use of oral laxatives, necessitating drug discontinuation (61). Selective 5-HT3-receptor antagonists cause constipation. They antagonize the ability of 5-HT to evoke cholinergically mediated contractions of the intestinal longitudinal muscle (62).

One of the most striking pharmacological features of opioids is their ability to cause constipation. Opioids cause constipation by binding to specific opioid receptors in the enteric and central nervous system. Opioid receptors have been identified on gut smooth muscle, suggesting that there is a local effect of opioid drugs, although central opioid effects cannot be excluded. Opioids affect the intestines by different mechanisms. Opioids augment the tone and nonpropulsive motility of both the ileum and the colon, thereby increasing transit time. Opioids desiccate the intraluminal content, either reducing secretion and increasing intestinal fluid absorption, with an indirect mechanism, possibly by tryptaminergic neurons in the myenteric plexus, resulting in the release of noradrenaline, which antagonize the secretory mechanism of the enterocytes, regulated by a-2 adrenoreceptors. Opioids may also suppress the release of the vasointestinal peptide, an inhibitory neurotransmitter. Vasointestinal peptide is a potent colonic secretagogue and an important inhibitor of smooth muscle contraction. Moreover, the prolonged bowel transit on its own may facilitate the increased intestinal absorption of fluid and electrolytes. Opioid use may lead to fecal impaction, spurious diarrhea, and bowel pseudo-obstruction, causing abdominal pain, nausea and vomiting, and interference with drug administration and absorption (19).

Oral morphine invariably causes constipation when used in repeated doses to treat cancer pain. Other common unwanted effects, such as sedation, nausea, and vomiting, tend to improve with continued use and often resolve completely. In contrast, it is commonly believed that opioid-induced constipation does not get better with repeated administration. However, long-term data suggest that a proportion of patients may become tolerant to the constipating effects of morphine with repeated administration (63). Other factors can contribute to slow intestinal transit, such as immobility, concomitant medications, disease-related factors, and so on. The importance of other factors for the development of constipation is demonstrated by the fact that approximately 50% of hospice patients not on opioids required regular oral laxatives (64). In another survey of patients admitted to hospice, 64% of patients not receiving opioid analgesia required laxatives.

The dose of laxative required seems to be significantly higher if an opioid is being taken than if not (65). Although there is no correlation between the dose of opioids and the dose of laxatives (63,64), an upward titration of laxatives in parallel to increasing doses of morphine has been observed (44). However, proportionally less laxative is required at a higher opioid dose. Approximate equivalents of laxatives and typical requirements of opioid therapy have been proposed, but there is clearly large individual patient variation (2).

Postoperative pain relief by both parenteral or intraspinal opioids is often associated with adynamic ileus. Gastric emptying and small bowel transit are inhibited. This is an important consideration for cancer patients undergoing surgical procedures in which the ileus is likely to be a severe problem. Epidural anesthesia with local anesthetics appears to disrupt gastrointestinal motility less than systemic opioids (6).

Assessment

There is evidence that the assessment and management of this symptom is frequently neglected by physicians and nurses. A minimal documentation on symptoms of constipation has been found in palliative care surveys (66). A careful history should be taken regarding the onset of constipation, bowel habits, and the use of laxatives. Patients who develop progressive constipation in the absence of any clear precipitating cause should be considered for an evaluation that may include determination of electrolytes and renal and hepatic function tests.

It is of paramount importance to first establish what the patient means by constipation: if stools are too small, too hard, too difficult to expel, too infrequent, or if patients have a feeling of incomplete evacuation after defecation. Impaction with overflow should be excluded by performing a rectal examination. Therefore, the first step is to completely evacuate the bowel. Multiple oil or saline enemas may be needed. Digital fragmentation is unpleasant, but may permit the great majority of fecal impactions in the rectum to be diagnosed. A pseudo-diarrhea in the presence of impaired anal sphincter function may be discovered. Gentle digital examination of the rectum may reveal a hard mass, a rectal tumor, rectal ulcers, an anal stenosis, anismus, or a lax anal sphincter. Patients with spinal cord lesions may have reduced sensation, but the anal tone is preserved, whereas patients with sacral nerve root infiltration will have a reduced anal tone. The examination of the abdomen may reveal fecal masses in the left iliac fossa. Fecal masses are usually not tender, are relatively mobile, and can be indented with pressure.

An abdominal radiograph may distinguish between constipation and obstruction. Examination after a barium meal may help to distinguish between paralytic ileus and mechanical obstruction. Barium studies may help reveal a small intestine motility dysfunction in chronic intestinal pseudo-obstruction. In visceral myopathy, intestinal contractions are infrequent, whereas with a visceral neuropathy, patients tend to have less distention and faster intestinal transit time due to uncoordinated contractions (59).

When constipation is due to ineffective colonic musculature, measurement of colonic transit time may be a useful tool to detect specific areas of the bowel that are not functioning properly. Pieces of radiopaque nasogastric tube are ingested and the progression of markers along the colon is observed by a daily radiograph until total expulsion. This study may demonstrate a delayed transit in the colon, a long storage of feces in the rectum, or a retrograde movement due to a distal spasm (67). A radiological constipation score has been proposed, assessing the amount of stool in each of the four abdominal quadrants (66).

Treatment

The management of constipation can be divided into general interventions and therapeutic measures. An extensive effort should be made to find a specific cause of constipation, and then treatment can be directed at that cause. Etiologic factors, such as physiologic consequences of cancer-associated debility, biochemical abnormalities, including hypercalcemia and hyperkalemia, and drug use, should be identified and reversed wherever possible. An adequate fluid intake is helpful to increase the stool water content (68).

Fluids, fruit juice, fruit, and bran are all recommended. However, fiber deficiency is unlikely to account for a lower stool weight, and there is no justification for the claim that treatment with bran can return stool output and transit time to normal. In far-advanced cancer patients, the use of high amounts of fiber is beyond the capacity of most patients (69). Moreover, dietary fiber seems to have no prophylactic value to prevent constipation in hospitalized patients. Fiber consumption may relatively decrease fluid intake, thus paradoxically worsening the situation (6).

As an unfavorable toilet environment, such as lack of privacy or inappropriate posture, may lead to constipation, patients should be provided privacy and appropriate facilities in the hospital setting.

When irreversible causes of constipation cannot be directly treated, symptomatic relief should be provided. Moreover, in spite of prophylaxis, most of these patients will require chronic laxatives, especially in the advanced stage of their disease or when treated with chronic opioid therapy. It is appropriate to begin prophylactic laxative treatment in patients with risk factors for constipation, including the elderly, those who are bedridden, or those requiring drugs known to cause constipation (70).

A low-rectal impaction should be removed manually. Appropriate sedation and analgesics are usually required to make this procedure comfortable. A more proximal mass can be broken by a sigmoidoscope or by delivering a pulsating stream of water against the stool. The use of enemas and rectal interventions is limited to the acute short-term management of more severe episodes. Therapeutic interventions for the management of constipation are based on the administration of laxatives, either orally or rectally. Laxatives are commonly used in advanced cancer patients. Sixty-two percent of patients admitted to hospice received laxatives regularly (64). Laxatives will promote active electrolyte secretion, decrease water and electrolyte absorption, increase intraluminal osmolarity, and increase hydrostatic pressure in the gut. Although laxatives can be divided into several groups, no agent acts purely to soften the stool or to stimulate peristalsis. Clinical criteria, responsiveness, acceptability, and the patient's preference should guide the selection of the drug. Table 15-3 outlines different medications useful for constipation.

Drug	Category	Comments
Docusate	Stool softener	Acts in 1–3 d, prevents hard stool formation, not together with mineral oil
Mineral oil	Lubricant	Useful in acute impaction
Senna	Contact	Acts on distal colon after conversion
Cascara	Contact	Dose-related colics
Bisacodyl	Contact	Effective within 12–24 h
Lactulose	Osmotic	Dose-related cramps, gaseous distention, effective after 2 d, useful in hepatic encephalopathy
Magnesium salts	Osmotic	Rapid evacuation, not in renal failure
Cisapride	Prokinetic	Mild laxative effect, anticholinergics may decrease cisapride's effects
Naloxone	Opioid antagonist	Possible withdrawal syndrome

TABLE 15-3. DIFFERENT MEDICATIONS USEFUL FOR CONSTIPATION

Laxatives

Patients with advanced cancer are likely to have chronic constipation and will need continuous laxative treatment. No data exist to guide the clinician or patient in the optimal choice of laxatives, as there have been no adequate comparative studies of long-term management of opioid-induced constipation. One of the main limitations of such trials is the lack of reliable clinical assessment tools. In a randomized, crossover clinical trial of laxatives in a hospice, lactulose/senna combination produced a significantly greater stool frequency than codanthramer in patients receiving opioids and reduced the usage of rectal measures, although the penalty for this achievement was an increased likelihood of diarrhea (71). In a comparative study conducted with the objective of determining treatment and cost efficiency for senna and lactulose in terminal cancer patients treated with opioids, no difference was found between the laxatives in defecation-free intervals or in days with defecation (72). In a recent systematic review, the use of docusate for constipation in palliative care has been found to be based on inadequate experimental evidence (73). In a study of healthy volunteers, in which constipation was induced by loperamide, a combination of stimulant and softening laxatives was most likely to maintain normal bowel function at the lowest dose and least adverse effects. Senna was associated with significantly more adverse effects than the other laxatives (74).

Bulk-Forming Agents

Bulk-forming agents are high-fiber foods containing polysaccharides or cellulose derivatives resistant to bacterial breakdown. These agents increase stool bulk and correct its consistency by increasing the mass and the water content of the stool. Evidence of their effect may take 24 hours or more. Their effectiveness and feasibility in the advanced cancer patient are doubtful, as they require the patients to drink extra fluids to prevent viscous mass formation.

Emollient Laxatives

Emollient laxatives are surfactant substances not adsorbed in the gut, acting as a detergent and facilitating the mixture of water and fat. They also promote water and electrolyte secretion. Stimulant laxatives are the most commonly used drugs to treat constipation. They are represented by the anthraquinone derivatives, such as senna, cascara, and danthron, and the diphenylmethane derivatives, such as bisacodyl and phenolphthalein. This class of drugs acts at the level of the colon and distal ileum by directly stimulating the myenteric plexus. Senna is converted to an active form by colonic bacteria. As a consequence, its site of action is primarily the colon. Danthron and the polyphenolic agents bisacodyl and sodium picosulfate undergo glucuronidation and are secreted in the bile. The enterohepatic circulation may prolong their effect. An increase in myoelectric colonic activity has been observed after administration of oral senna. Bisacodyl stimulates the mucosal nerve plexus, producing contractions of the entire colon and decreasing water absorption in the small and large intestine. Castor oil is metabolized into ricinoleic acid that has stimulant secretory properties and an effect on glucose absorption. All of these drugs may cause severe cramping. The cathartic action occurs within 1–3 days. Starting doses proposed are 15 mg daily of senna, 50 mg daily of danthron, or 10 mg daily of bisacodyl. Bisacodyl suppositories promote colonic peristalsis with a short onset due to the rapid conversion to its active metabolite by rectal flora. Docusate alone or in combination with danthron is most commonly used at doses of 100–300 mg every 8 hours. The effectiveness of docusate has been questioned (69).

Lubricant Laxatives

Lubricant laxatives are represented by mineral oil. It may be useful in management of transient acute constipation or fecal impaction, but has a little role in the management of chronic constipation. It lubricates the stool surface. Coated feces may pass more easily and colonic absorption of water is decreased. It may also decrease absorption of fat vitamins. Absorption of small amounts may cause foreign-body reactions in bowel lymphoid tissue. Liquid paraffin, 10 cm^3 day, may be given orally or rectally with an effect noted in 8–24 hours.

Hyperosmotic Agents

Hyperosmotic agents are not broken down or absorbed in the small bowel, drawing fluid into bowel lumen. Lactulose increases fecal weight and frequency but may result in bloating, colic, and flatulence, as well as electrolyte imbalances at high doses. Moreover, it is expensive in comparison to other preparations. The latency of action is 1–2 days. Starting doses are 15–20 ml twice a day. Saline laxatives exert an osmotic effect, increasing the intraluminal volume. They also appear to directly stimulate peristalsis and increase water secretion. The starting dose is 2–4 g daily. Magnesium, sulfate, phosphate, and citrate ions are the ingredients in saline laxatives. Saline laxatives usually produce results in a few hours. Their use may lead to electrolyte imbalances with accumulation of magnesium in patients with renal dysfunction or an excessive load of sodium in hypertensive patients. Moreover, their administration may result in an undesirable strong purgative effect. Administered rectally, they stimulate rectal peristalsis within 15 minutes. Repeated use of a phosphate enema may cause hypocalcemia and hyperphosphatemia or rectal gangrene in patients with hemorrhoids. Glycerin can be used rectally as an osmotic and lubricant agent.

Prokinetic Drugs

Cisapride is a prokinetic agent that appears to accelerate orocecal transit and to stimulate the colon. Cisapride enhances the release of acetylcholine from the myenteric nerve endings. It is devoid of the central antidopaminergic effects that limit the use of metoclopramide. It has been shown to correct impaired propulsion in the small bowel of patients with pseudo-obstruction. Suggested doses are in the range of 2.5–10 mg four times a day. Metoclopramide given by the subcutaneous route, but not by oral route, seems to be effective in narcotic bowel syndrome. Effects of metoclopramide are mediated by a central and peripheral antidopamine effect, and a stimulation of cholinergic receptors (19).

Opioid Antagonists and Opioid Therapy Modification

Opioid-induced constipation can be severe and refractory to therapy with conventional laxatives. Opioid concentration in the enteric nervous system correlates better with opioid-induced, prolonged, intestinal transit time than concentrations in the central nervous system (75,76). Naloxone is a competitive antagonist of opioid receptors inside and outside the central nervous system and, after systemic administration, it reverses both centrally and peripherally mediated opioid effects. There is now evidence that oral administration of naloxone can reverse opioid-induced constipation, without causing systemic opioid withdrawal in most patients. This route of administration theoretically allows selective blocking of intestinal opioid receptors without blocking the desired opioid effects, as long as hepatic first-pass capacity is not exceeded. The low systemic bioavailability due to marked hepatic first-pass metabolism allows for the low plasma levels and high enteric wall concentration (75). Oral administration of naloxone at a daily dose of approximately 20% of the daily morphine dose is capable of providing a clinical laxative effect without antagonizing opioid analgesia (77). In another study, the mean dose of naloxone was 17.5 mg/day. Adverse effects of short duration, including yawning, sweating, and shivering, were observed in approximately one-third of patients (78). While oral naloxone doses below 2–4 mg, or 10% or less of the morphine dose are mostly ineffective (78,79), opioid withdrawal may present. Reversal of analgesia does not seem to be an early symptom of systemic opioid antagonism (79).

In the former reports, the naloxone dose has been based on the preexisting morphine dose and expressed in percentages of daily morphine (75,76,77,78 and 79). However, the reaction to opioid antagonists seems to be proportional to the degree of opioid tolerance rather than to opioid concentration, and the risk of systemic withdrawal may increase if the same percentage relationship is used in patients with high opioid doses (80). It has been suggested that the initial dose of naloxone should not exceed 5 mg (75). Dose titration, beginning with a dose of 0.8 mg twice daily and doubling the dose every 2 to 3 days until favorable effects occur or adverse effects are experienced, independently of the preexisting morphine usage, may be a reasonable approach (75,81). Methylnaltrexone is an opioid antagonist that cannot penetrate the blood–brain barrier and has been shown to reverse morphine-induced delay of gastric emptying and intestinal transit time after intravenous infusion in volunteers (82). In a pilot study of subjects receiving chronic methadone therapy, low doses of intravenous methylnaltrexone effectively reversed chronic methadone-induced constipation and delay in gut transit time (83). It deserves future studies in cancer patients with opioid-associated constipation.

Constipation is an adverse effect that rarely requires modification of opioid therapy. However, there is a rationale in changing the route of administration. The use of a parenteral administration should result also in a change of the opioid concentration at intestinal receptors. However, in a retrospective study no difference in the doses of laxatives required to maintain regular bowel movements in patients receiving oral versus subcutaneous opioids was found (84).

Among opioids there may be differences in the analgesia/constipation ratio. Clinical studies have revealed that at doses of oral morphine and transdermal fentanyl that yield equivalent pain relief, constipation differs significantly between the two drugs (85,86,87 and 88). Although the majority of early studies were not randomized, different methodologies were used, and the analysis was performed while switching patients from oral morphine to transdermal fentanyl, more recent trials are remarkably consistent in that transdermal fentanyl causes less constipation than oral sustained-morphine at the same level of analgesia (89).

Differences in pharmacological profiles, in the affinity to opioid receptor and a higher exposure of opioid-binding receptors in the gastrointestinal tract following oral administration of morphine compared with transdermal administration of fentanyl, may offer an explanation for the clinically observed different constipation-inducing potentials of equipotent doses of morphine and fentanyl. The lipophilicity profile of fentanyl allows for the ease with which fentanyl penetrates the brain. As less opioid is required to produce a central analgesic effect, less opioid is available in the peripheral circulation to induce constipation. Experimental studies using a castor-oil–induced diarrhea model have shown a more favorable analgesia/constipation ratio of subcutaneous fentanyl as compared with oral morphine, although the difference was less pronounced with oral fentanyl. Considerably larger amounts of naloxone were needed to reverse the morphine than the fentanyl-induced antidiarrheal effects (90).

Methadone has a high oral bioavailability, a rapid and extensive distribution phase, followed by a slow elimination. The end of the distribution phase is at or below the minimum effective concentration necessary for an effect. This may result in limiting the continuous bathing of intestinal receptors. The high lipophilicity of methadone allows for the maintenance of a low plasma concentration with a relevant clinical effect. Constipation seems to be the symptom that mostly improves after opioid switching (91). This could be simply due to different tolerance of different opioid at the level of receptors located in the bowel. Moreover, different reports have shown that methadone therapy may cause less constipation than morphine (92,93). In a retrospective analysis, the laxative/opioid dose ratio was lower in patients receiving methadone than in patients on morphine (94).

Therapeutic Strategy

Local measures to soften fecal mass are necessary in case of rectal impaction. The short latency of action of rectal laxatives may be useful to remove hard feces impacted in the rectum. Glycerin suppositories or sorbitol enemas soften the stool by osmosis, also lubricating the rectum wall. Water penetration may be facilitated by a stool softener. Saline enemas cannot be regularly administered and should be used as a last resort if suppositories fail. Any patient requiring an enema should be reevaluated for a possible laxative dose titration.

Practical and economic consideration may influence the choice of drug according to the setting (home, hospital, hospice, or palliative care unit). While stimulant agents may cause painful colic, softener drugs may be useful in the presence of a hard stool. Peristaltic stimulants are indicated in patients unable to pass soft stool. Senna is the most useful drug in the presence of soft feces in the rectum. All patients commencing opioid analgesia should have a prophylactic laxative unless a contraindication exists, although periodic laxative-free intervals have been advocated for patients with a relatively long prognosis to avoid tolerance (70,81).

Laxative dose should usually be titrated according to the response and not according to the dose of opioids. The opioid dose increments do not determine laxative efficacy, indicating that constipating effect of opioids is not a function of dose. Combination therapy with different mechanisms may be more useful when higher doses of one laxative are required (72). In patients suspected of having intestinal obstruction, laxatives with a softening action may be tried (64). However, treatment should be immediately interrupted when transit stops. Patients with colostomies require the same treatment. Before using stimulating agents, an obstruction should be excluded in the absence of feces in a colostomy. Paraplegic patients often require regular manual evacuation. Glycerin and bisacodyl suppositories should be given in patients with cauda equina syndrome. They may also benefit from the use of cisapride. Opioid switching may be indicated in cases in which there are serious therapeutic difficulties in maintaining bowel transit. Opioid switching as well as the use of opioid antagonists should be carefully monitored.

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16

BOWEL OBSTRUCTION

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BACKGROUND

Abdominal symptoms in oncology patients are quite common. Opioids, chemotherapeutic agents, and tumor can lead to abdominal pain, constipation, and vomiting. These symptoms are frequent and can be confused with mechanical bowel obstruction. Bowel obstruction may be a primary presentation or secondary complication of a malignancy. Bowel obstruction can involve either the upper or lower gastrointestinal tract, and the site of obstruction determines management. Initial management is generally conservative and consists of hydration and nasogastric decompression. The decision to proceed with surgical intervention needs to be individualized to each patient. It is one of the more frequent reasons for emergency abdominal surgery in cancer patients (1,2).

Palliative management of bowel obstruction is often required in the oncology patient. Determining the course of palliative therapy can be challenging, and one must balance the individual patient's needs and desires with clinically sound judgment. Oncology patients can either be palliated medically or surgically. End-stage patients and patients who are not surgical candidates should receive medical palliation.

INCIDENCE

Upper gastrointestinal obstruction in the general population is more commonly caused by malignancy than ulcer disease, as a result of the introduction of proton pump inhibitors and H_2 blockers (3,4). Gastric carcinoma is the most common malignancy causing gastroduodenal obstruction, followed by pancreatic carcinoma (4). Obstruction is the initial presentation in 17.5% of patients with gastric cancer (5). Patients with pancreatic cancer initially present with upper gastrointestinal obstruction 6% of the time (6). After diagnosis, the incidence of gastroduodenal obstruction increases (7,8). In a review of 350 patients with pancreatic cancer, 25% of patients with unresectable disease developed gastroduodenal obstruction (6).

In contrast to gastroduodenal obstruction, small bowel obstruction in the general population is less commonly the result of malignancy. In a review of 238 patients with a diagnosis of small bowel obstruction, malignancy was the third most common cause of obstruction (7%) behind adhesions and hernia, accounting for 88% (9). The incidence of small bowel obstruction is much higher in the cancer population and is generally secondary to cancers arising at other sites. In a review of 518 patients with ovarian cancer, 127 patients (14%) developed intestinal obstruction (10). A direct correlation was reported between the stage of disease and the frequency of obstruction. In colorectal cancer, 41 of 472 (10%) patients developed small bowel obstruction after primary resection of their cancer (11).

Unlike small bowel obstruction, acute colonic obstruction in the general population is caused by primary malignancy of the colon in the majority of patients. Primary colorectal carcinoma was the cause of colon obstruction in 53% of 300 patients, whereas only 6% of obstructions were caused by extrinsic compression of the colon from metastases (12). In another study of 127 patients presenting with acute colonic obstruction, 99 (78%) were caused by primary colon cancer and 15 (12%) were caused by noncolonic carcinoma (13).

ETIOLOGY

In the majority of oncology patients, symptoms of nausea, vomiting, abdominal pain, and constipation are nonobstructive in origin. Certain chemotherapeutic agents cause nausea and vomiting as well as constipation. Vincristine sulfate may cause constipation or adynamic ileus. Forty-six percent of patients receiving vincristine sulfate, in one series, reported constipation, abdominal pain, or both (14). Nonchemotherapeutic agents (e.g., narcotic analgesics and anticholinergics) may lead to adynamic ileus. Also, patients with malignancy often are bedridden, inactive, malnourished, dehydrated, and have electrolyte imbalances. These states can lead to bowel dysmotility and the resultant clinical presentation may mimic mechanical bowel obstruction.

When present, mechanical bowel obstruction may involve the upper or lower gastrointestinal tract. The anatomical sites of obstruction in three combined series were small bowel (48%), colorectal (37%), both (4%), and gastroduodenal (11%) (15,16 and 17). Gastroduodenal obstruction is rarely benign in nature in the oncology patient. The obstruction may be secondary to a primary stomach cancer or by direct extension from kidney, pancreas, biliary, or colon carcinoma. Ovarian carcinoma can lead to gastroduodenal obstruction as well (18).

In contrast to gastroduodenal obstruction, a significant percentage of small bowel obstructions occurring in the cancer patient are benign. In the reviewed series, a median of 32% of small bowel obstructions were the result of benign processes such as adhesions from previous oncological operations (Table 16-1). However, the majority of small bowel obstructions (59–100%) were caused by recurrence of intraabdominal malignancy. Few patients present with primary small bowel tumors as the cause of obstruction (19). A primary small bowel tumor (adenocarcinoma, sarcoma, carcinoid, and lymphoma) should be suspected in patients with abdominal pain, weight loss, and occult gastrointestinal bleeding (20). Metastatic small bowel lesions should be considered in patients with these symptoms along with a history of cancer of the ovary, colon, stomach, pancreas, and breast, or melanoma.

			Etiology (%)		Medical treatment (%)		Surgical treatment (%)			
Author (reference)	Patients	Histology	Benign	Malignant	Success	Recurrence	Success	Recurrence	Morbidity	Mortality
Ketcham 1970 (29)	117	All	18	82	–	–	–	33	–	16
Elias 1973 (28)	98	All	–	–	29	45	56	9	–	–
Ahmed 1979 (3)	34	All	3	97	–	–	79	23	44	18
Ottesen 1980 (24)	66	All	39	59	29	32	80	14	15	9
Aravena 1981 (22)	73	All	11	89	–	–	84	–	24	35
Ashe 1984 (15)	41	Nongynecologic	17	83	–	–	73	–	–	24
Walsh 1984 (27)	53	All	32	68	–	–	96	–	–	13
Gallick 1986 (25)	84	All	24	76	12	41	88	23	–	13
Butler 1991 (26)	54	All	32	68	28	45	76	11	49	16
Wakeley 1991 (17)	65	All	0	100	–	–	55	13	42	23
Tang 1995 (51)	61	All	39	61	29	40	72	33	16	12
Nakano 1996 (28)	65	Gastric	23	80	21	–	48	–	–	6
Woolfson 1997 (18)	75	Nongynecologic	36	64	29	3	76	16	–	33
Ishii 1998 (11)	41	Colorectal	33	49	–	–	90	–	–	17
Median	79		28	74	29	41	79	16	31	16

TABLE 16-1. INTESTINAL OBSTRUCTION IN PATIENTS WITH A PREVIOUS DIAGNOSIS OF MALIGNANCY

Colorectal, ovarian (gynecological), and gastric are the most common (nearly three-fourths) sites of primary tumor in patients with subsequent small bowel obstruction (15,17,21,22,23,24,25,26,27,28 and 29). Less frequent are a variety of other intraabdominal and extraabdominal sites of tumor [e.g., pancreas (15,17,21,22,23,24 and 25), melanoma (21,22,30), breast (21,23,24), lung (21,22,23,24 and 25,31), and mesothelioma (22,23 and 24)]. Melanoma is the most common cause of malignant intussusception in the adult population (32). Thus, small bowel lesions may cause obstruction by their intraluminal occlusion, extraluminal compression, or by

intussusception (20,30,33).

Colorectal cancer can lead to obstruction of the colon as well as small bowel obstruction. Primary large bowel obstruction is most commonly caused by colon carcinoma (78% of patients) (13). Noncolonic malignancy (12%) and benign causes (10%) account for the rest. Approximately 15–20% of patients with colon carcinoma present with obstruction (34,35,36 and 37). Due to the increased diameter of the right-sided colon and the fecal consistency, left-sided colon cancer obstructs more readily than right-sided malignancies. Intussusception is an infrequent mechanism of obstruction in these patients (13,38). Ovarian and prostate carcinoma may obstruct the colon by peritoneal carcinomatosis or direct extension, respectively. Twelve percent of 379 patients with ovarian carcinoma developed rectosigmoid obstruction (39). Extraabdominal cancers, such as breast cancer metastases, may lead to large bowel obstruction (40).

As mentioned previously, not all bowel obstructions in cancer patients are mechanical in nature. A patient presenting clinically with obstructive symptoms may have intestinal dysmotility or pseudo-obstruction. The pathophysiology of pseudo-obstruction in the oncology patient has been attributed to denervation of the bowel and mesentery by carcinoma, metastatic infiltration of the celiac plexus, and paraneoplastic syndromes (41). Ogilvie's syndrome, classically described, specifically refers to pseudo-obstruction as a result of extraabdominal metastatic carcinoma invading the celiac plexus leading to sympathetic denervation (42). Small cell carcinoma of the lung, malignant thymoma, and retroperitoneal leiomyosarcoma have all been associated with intestinal pseudo-obstruction (41,43,44). These patients were all noted to be free of gastrointestinal involvement by their tumors at exploratory laparotomy despite obstructing symptoms. Recently, antibodies have been identified in small cell lung carcinoma that preferentially bind to neuronal elements in the small bowel (45).

DIAGNOSIS

After a careful history and physical examination are performed and blood is obtained for studies, patients admitted with obstructive symptoms (e.g., nausea, vomiting, constipation, crampy abdominal pain, and abdominal distention) should undergo radiographical evaluation with plain films of the abdomen (supine and upright) and chest. Patients with nondiagnostic plain abdominal films, atypical history or physical examination, or protracted courses without resolution of obstructive symptoms are candidates for further studies.

When a small bowel obstruction is suspected but not confirmed radiographically, abdominal computed tomography (CT) may be helpful. As many as 34% of patients with obstructive symptoms may have indeterminate or equivocal plain radiographs, resulting in delayed management (46). In this patient population, an abdominal CT scan is invaluable for diagnostic accuracy. In a recent study of 32 patients presenting with clinical suspicion of intestinal obstruction, abdominal CT had a higher sensitivity (93%) and specificity (100%) than plain radiographs (77% and 50%, respectively) in diagnosing obstruction (47). Therefore, an abdominal CT should be reserved for patients with an unclear diagnosis after plain films.

Upper gastrointestinal radiographic contrast studies with small bowel follow-through may be useful in further delineating a small bowel obstruction. Barium is generally more useful than water soluble contrast agents for identifying a distal obstruction because it does not become diluted by gastrointestinal secretions. If barium remains in the small bowel, it does not become inspissated because the small bowel lacks the water absorptive capacity of the colon. However, a disadvantage of barium studies is the need to cleanse the bowel of this agent before performing subsequent CT scans. Perhaps the greatest benefit of the upper gastrointestinal series is in patients with intermittent or partial small bowel obstruction.

For patients with suspected colonic obstruction, or both small and large bowel obstructions and no perforation, barium enema can be quite useful in determining the presence of large bowel obstruction. In 79 patients with suspected mechanical large bowel obstruction by plain abdominal radiograph, contrast enema confirmed the diagnosis in 50 patients (63%). However, one-third had free flow of contrast and were not obstructed (48). In another study, 35 of 99 patients (35%) with suspected mechanical large bowel obstruction by abdominal radiographs were found to be nonobstructed by contrast enema. In 11 of these 35 patients, colonic pseudo-obstruction was diagnosed (49). A barium enema should be terminated promptly if the fluoroscopist detects an obstructing lesion. The colon can absorb water from the barium, which then becomes inspissated above a partially obstructing lesion, making subsequent colonic cleansing very difficult.

MANAGEMENT OF MECHANICAL OBSTRUCTION

Overview

An algorithm describing the management of a suspected malignant mechanical bowel obstruction is presented in Figure 16-1. At initial presentation, a history, physical examination, and abdominal plain films should be routinely performed. Obstructed patients are usually dehydrated and have electrolyte imbalances due to persistent vomiting and the inability to tolerate oral liquids. All patients should be aggressively intravenously hydrated and given nothing by mouth. A nasogastric tube should be placed to relieve obstructive symptoms and electrolytes should be determined and corrected. Once the patient is adequately stabilized and hydrated, therapeutic strategies can be entertained.

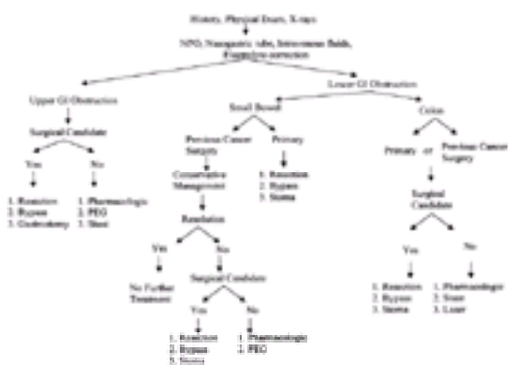


FIGURE 16-1. Management algorithm for malignant bowel obstruction. GI, gastrointestinal; NPO, nothing by mouth; PEG, percutaneous endoscopic gastrostomy.

When an upper gastrointestinal obstruction is diagnosed, the etiology is generally secondary to a malignancy. If the patient is able to tolerate an operation, a resection and anastomosis or a gastroduodenal bypass should be performed. If the patient is not a surgical candidate, pharmacological palliation or less invasive medical procedures can be offered.

In the setting of small bowel obstruction, patients with a previously resected malignancy may be managed with a trial of conservative therapy. If the obstruction resolves, no further treatment is warranted. If the obstruction persists for greater than 3–7 days, patients that are not surgical candidates are managed pharmacologically. Patients able to tolerate an operation should undergo an exploratory laparotomy with the intention of reestablishing gastrointestinal continuity. The procedure may involve enterolysis for benign obstruction, or resection, bypass, or a diverting ostomy for recurrent cancer.

In contrast to small bowel obstruction, mechanical colonic obstruction is not managed initially by a trial of conservative therapy. If the patient is able to tolerate an operation, a resection should be attempted when feasible. Patients with large tumor burden can be managed either by bypass or stoma creation. Patients unable to tolerate a surgical procedure can be managed pharmacologically or by less invasive laser therapy or stenting.

Initial Management

In the absence of fever, leukocytosis, or peritonitis, patients with obstructive symptoms deserve a trial of conservative therapy. Patients need to be monitored with serial physical examinations (preferably by the same clinician) and with daily abdominal radiographs. Such treatment in nonselected cases of partial small bowel obstruction may result in resolution of symptoms in up to 88% of patients (50). In the oncology patient, nasogastric decompression, intravenous hydration, and electrolyte replenishment results in spontaneous resolution of small bowel obstructions in 12–29% of patients (Table 16-1) in a mean of 3–7 days (24,25 and 26). Forty-one percent of patients (median) need to be readmitted for conservative or surgical management of recurrent obstruction (Table 16-1). Bowel strangulation and gangrene is rare in these circumstances (0–5%) (21,23,24 and 25,51), with the exception of one series, in which it occurred in 24% of patients (26). Preoperative recognition of bowel strangulation cannot be done reliably in patients with complete mechanical obstruction (52).

The choice of nasogastric tube or long intestinal tube (i.e., Miller-Abbott, Cantor, Baker) for decompression is individualized by the physician. Both tubes have been reported to have similar success in complete small bowel obstruction (53,54), although long tubes were associated with longer hospitalization (54). A recent randomized

study has failed to identify the superiority of one tube over the other (55). Partial small bowel obstruction has a higher success rate (88%) when treated with nasogastric decompression. A long tube yielded similar results as treatment with a nasogastric tube (50). The most common practice is to use the nasogastric tube because of its ease of placement and effectiveness in decompressing the upper gastrointestinal tract. Long tubes are more difficult to get into position (i.e., pass beyond the duodenum) but can be effective in decompressing the more distal bowel. They may be useful in delineating a site of obstruction by failing to pass beyond the obstructed point or serving as a port for instillation of radiographic contrast agents. Long tubes may also prove useful intraoperatively when faced with carcinomatosis and dense adhesions. Locating a suitable segment of small bowel for bypass may be facilitated by this tube.

Therefore, when managing patients with small bowel obstruction after oncologic surgery, an initial trial of conservative therapy is warranted in clinically stable patients. If the patient deteriorates or fails to improve after a clinically acceptable length of therapy, surgical therapy can be offered.

Surgical Management

Gastroduodenal

When patients present with gastroduodenal obstruction, the goal is to reestablish gastrointestinal continuity with curative intent or at least provide palliation. Surgical resection (if possible) or, alternatively, bypass should be undertaken. Only 15% of pancreatic patients are resectable for cure at time of diagnosis (56) and less than 20% of patients survive for more than 1 year after diagnosis (57). Therefore, palliative procedures are of primary importance in this patient population. Thirteen percent to 21% of patients with pancreatic cancer who do not undergo a gastrojejunostomy at initial exploration eventually do require a gastrojejunostomy for palliation of gastric outlet obstruction (8,56,58). Due to these findings, many favor prophylactic gastrojejunostomy at the time of initial exploration, once unresectability is determined (7,8,59). Palliation is not always achieved with gastrojejunostomy. Delayed gastric emptying may occur after the procedure, leading to significant postoperative morbidity (7,60,61). Recently, laparoscopic gastroenterostomy has been introduced for the treatment of gastroduodenal obstruction. The procedure can be performed safely with minimal operative times. Good palliation of nausea and vomiting can be expected (62,63).

Small Intestine

As many as one-third of cancer patients undergoing surgery for small bowel obstruction with a previous diagnosis of cancer may have adhesions or a benign cause of obstruction (Table 16-1). In this setting, operative success in resolving their symptoms is usually high. Still, the majority of obstructions in patients with a previous cancer diagnosis are tumorrelated (median, 74%). Forty-eight percent to 96% of patients (median, 79%) can be surgically relieved of their symptoms. A variety of surgical procedures have been performed to relieve the small bowel obstruction (Table 16-2). Bypass is the most commonly performed procedure, followed by stoma creation and then resection. Recurrent obstruction after successful surgical relief of symptoms occurs in 9–33% of patients (Table 16-1). Operative morbidity (median, 31%) and mortality (median, 16%) are high and reflect the generally ill nature of this patient population. Treatment options are similar for a small bowel obstruction caused by a primary small bowel tumor or an extraabdominal carcinoma with a metastasis to the small bowel. Patients should be managed by resection with primary anastomosis, when appropriate, or by bypass, if resection is not warranted or possible.

Author (reference)	Surgical procedures	Bypass	Stoma	Resection	Enterolysis	Other
Ozsoy 1980 (24)	54	20	5	2	18	9
Aoba 1984 (1)	59*	20	19	11	5	1
Gollub 1986 (25)	59*	16	10	18	12	3
Cantu 1987 (10)	48	1	34	11	3	3
Butler 1991 (26)	49*	12	8	19	7	7
Maeda 1991 (27)	85	25	25	25	8	10
Tang 1995 (51)	67*	28	15	3	14	8
Nakano 1996 (28)	58	14	12	5	18	9
Ebihara 1998 (11)	41	7	1	16	16	1
Total	457	144	121	110	85	37

*More than one procedure in some patients.

TABLE 16-2. SURGICAL PROCEDURES TO RELIEVE OBSTRUCTION IN CANCER PATIENTS

Colon

The surgical management of right-sided and transverse colonic obstruction secondary to a primary colonic malignancy is similar to small bowel obstruction. Right hemicolectomy for obstructing right colon lesions or extended right hemicolectomy for transverse colon lesions followed by primary anastomosis is generally considered safe in emergent conditions without preoperative bowel preparation (13,36,64,65). Obstructing carcinoma of the splenic flexure can be managed by extended right hemicolectomy and immediate anastomosis (64,65), although including these lesions in a left colon resection is also a valid option. The best approach is one individualized for the patient and comfortable to the surgeon.

The surgical management of obstructing left colon and sigmoid lesions is evolving from the traditional three-stage procedure to a two-stage procedure and, most recently, a single-stage procedure (36,64,66,67). The presence of peritoneal soiling or inflammation, the condition of the bowel, the stability of the patient, and ultimately the judgment and expertise of the surgeon will dictate the approach used. All three methods have a role that depends on the clinical setting. The three-stage procedure for lesions distal to the splenic flexure involves (a) creation of a proximal (transverse colon) decompressing colostomy, (b) elective resection of the lesion in the mechanically cleansed bowel and primary anastomosis, and (c) colostomy closure.

Presently, a two-stage procedure is the more common approach and consists of primary resection with the creation of a proximal end colostomy and Hartman pouch or mucous fistula (36). The second stage reestablishes bowel continuity. Retrospective data as well as one randomized study (68) support the use of a two-stage as opposed to a three-stage approach.

The most recent trend in treating obstructing left colon lesions has been a single-step segmental resection and primary anastomosis in selected patients (63,69,70,71,72,73,74,75 and 76). Currently, onestage procedures for obstructing left colon lesions are not advocated in the presence of fecal peritonitis, a large continuous pelvic abscess, or systemic sepsis (66). To accomplish a onestage procedure in highly selected populations and maintain a low incidence of anastomotic leak, a variety of approaches that allow mechanical bowel cleaning have been advocated. Preoperative techniques include endoscopic laser relief of obstruction (77), passage of a rectal tube over guidewire (78), colonic irrigation via long intestinal tube (79), and percutaneous colonic irrigation (80). Intraoperatively, a technique of intracolonic bypass with a silastic and latex tube has been described (81). Gaining popularity is intraoperative colonic irrigation as advocated by a variety of groups (63,69,70,71,72,73 and 74). The technique consists of proximal (cecal) infusion of saline and distal (above the obstruction) collection of luminal contents in a closed system. After resection and mechanical cleansing, a primary anastomosis is performed. The most aggressive approach of subtotal/total colectomy and ileocolonic/ileorectal anastomosis obviates the need of mechanical bowel cleansing (34,82,83 and 84). The subtotal colectomy can decrease the operative time and complexity associated with colonic irrigation. Any synchronous tumors are removed as well.

The first prospective randomized multicenter trial comparing subtotal colectomy to segmental resection after intraoperative irrigation was recently completed (85). Mortality and complication rates did not differ significantly between the two groups. However, patients undergoing subtotal colectomy reported increased bowel movement frequency and increased visits to their general practitioners for bowel problems.

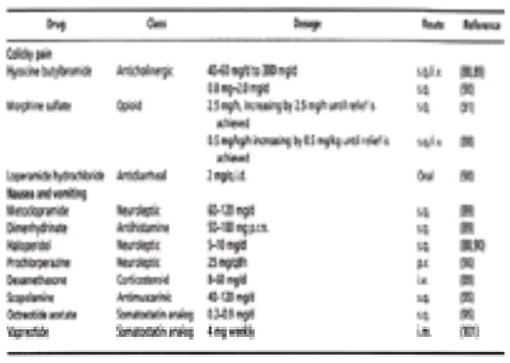
Curative resection for malignant colonic obstruction is not possible in all patients. Patients with unresectable disease, whether secondary to a primary, recurrence, or carcinomatous, may be palliated by bypass or stoma. For highrisk patients, a proximal diverting colostomy is still a viable alternative (86). Loop colostomies (independent of location) are generally easier to create and close than divided colostomies, and can be totally diverting (87).

Medical Management

Pharmacological

Pharmacological palliation is most often administered to end-stage cancer patients. The goal is to decrease symptoms associated with bowel obstruction. Therefore, pharmacological therapy should attempt to decrease abdominal pain, alleviate nausea and vomiting, reduce gastrointestinal secretions, and, at times, increase bowel motility. Hyoscine butylbromide and opioids (morphine sulfate) are the most frequently used agents to control colicky abdominal pain (Table 16-3) (88,89,90 and 91).

These agents may be delivered intravenously, rectally, or subcutaneously (92,93). Loperamide hydrochloride has also been used to relieve intestinal colic (90).



Drug	Class	Dosage	Route	Reference
Colicky pain				
Hyoscine butylbromide	Anticholinergic	40–60 mg/d to 300 mg/d	s.c./i.v.	[88,89]
		0.8 mg–2.0 mg/d	s.c.	[90]
Morphine sulfate	Opioid	2.5 mg/h, increasing by 2.5 mg/h until relief is achieved	s.c.	[91]
		0.5 mg/kg/h increasing by 0.5 mg/kg until relief is achieved	s.c./i.v.	[88]
Loperamide hydrochloride	Antidiarrheal	2 mg/q.i.d.	Oral	[90]
Nausea and vomiting				
Metoclopramide	Neuroleptic	60–120 mg/d	s.c.	[89]
Dimenhydrinate	Antihistamine	50–100 mg q.s.n.	s.c.	[89]
Haloperidol	Neuroleptic	5–10 mg/d	s.c.	[88,90]
Prochlorperazine	Neuroleptic	25 mg/q8h	p.r.	[90]
Dexamethasone	Corticosteroid	8–60 mg/d	i.v.	[89]
Scopolamine	Antimuscarinic	40–120 mg/d	s.c.	[95]
Octreotide acetate	Somatostatin analog	0.3–0.9 mg/d	s.c.	[95]
Vapreotide	Somatostatin analog	4 mg weekly	i.m.	[101]

TABLE 16-3. PALLIATIVE PHARMACOLOGICAL THERAPY

Emesis is controlled by a variety of different classes of pharmacological agents. Metoclopramide, dimenhydrinate, and haloperidol have all been administered subcutaneously to alleviate nausea and vomiting (88,89 and 90). Prochlorperazine (given rectally) and dexamethasone (given intravenously) have also been used (Table 16-3) (89,90).

For prophylaxis against crampy abdominal pain and nausea/vomiting, pharmacological agents have been employed that decrease gastrointestinal secretions. Hyoscine butylbromide, scopolamine, and octreotide acetate have all been used subcutaneously to successfully decrease gastrointestinal secretions (94,95). In one of these studies, the use of scopolamine or octreotide acetate led to the successful removal of nasogastric tubes in all 13 patients with end-stage cancer (95). Further, octreotide acetate may lead to a quicker resolution of symptoms related to bowel obstruction (95,96).

Continuous subcutaneous administration of octreotide acetate may reduce gastrointestinal secretions and control vomiting (97,98). Octreotide acetate exerts its effect by inhibiting the secretion of gastrointestinal enzymes, gastric acid, and water (98). Khoo and associates were the first to use octreotide acetate to palliate the symptoms of malignant bowel obstruction in 1992. Eighteen of 24 patients had a decrease in the amount of nasogastric tube aspirate and vomiting (99). Based on these results, octreotide acetate was used successfully to prevent the occurrence of complete bowel obstruction in two patients with partial bowel obstruction (100). Vapreotide, a new long-acting somatostatin analog, produces effects similar to octreotide acetate with weekly intramuscular administration (101).

Corticosteroids may have palliative effects because they are able to reduce the edema surrounding tumors (102). By reducing edema, steroids may lessen the extrinsic or intrinsic compression of the bowel lumen and relieve symptoms (102). A meta-analysis studying the use of corticosteroids and bowel obstruction could only conclude a trend towards the resolution of bowel obstruction at a dose range of 6–16 mg intravenously. Further study was recommended (103).

Optimal pharmacological management may permit the hydration of some terminally ill patients without the need for intravenous support. When the oral intake of fluids is contraindicated, the intravenous route may be used. Home care with intravenous hydration and pharmacological support has been successful in some series (104,105). However, intravenous access is often difficult in these patients. Hypodermoclysis is an option for hydration in terminally ill cancer patients. One liter of fluid can be administered subcutaneously in a safe and effective manner (106). Total parenteral nutrition is another option for hydration in this patient population. However, the risks from total parenteral nutrition are much greater than from simple hypodermoclysis (107).

Percutaneous Gastrostomy

When pharmacological management fails to control symptoms in patients that do not have surgical options, percutaneous endoscopic gastrostomy (PEG) may be an effective procedure to relieve symptoms of obstruction. PEG placement offers an alternative to nasogastric tube decompression and surgical gastrostomy when treating malignant upper gastrointestinal or small bowel obstructions. The PEG tube allows patients to resume oral intake and avoid nasogastric discomfort. In select patients with mostly gynecologic malignancies, palliation has been obtained successfully by PEG placement (108,109,110,111 and 112). In one study, 22 of 24 patients with advanced malignancies were able to tolerate liquids by mouth after PEG placement (5). Complications from PEG placement are mostly minor (e.g., superficial wound infections) (113). In addition, most patients can return home to continue palliative care (112,113).

Laser

Another palliative procedure less invasive than surgery for the relief of malignant bowel obstructions is endoscopic laser therapy. The laser has been used most frequently in select patients for left-sided colonic obstruction (77,114,115 and 116). The neodymiumyttrium aluminum garnet (Nd- YAG) laser is the most commonly used laser for palliation of symptoms. In a series of 117 patients treated with laser therapy for distal colonic obstruction, 89% of patients were successfully treated by initial endoscopic laser therapy. A mean number of seven sessions over a period of 7 months was needed to achieve long-term palliation in 65% of patients (116). Laser therapy has also been used concomitantly with metallic stents for distal colonic obstruction (117,118). After initial treatment of the obstruction with laser therapy, a metallic stent is inserted to increase colonic patency and decrease the need for repeated laser treatments (119). Obstructed patients with significant colorectal pain are best not treated by endoscopic laser therapy, as pain persists after treatment (116).

Stenting

Endoscopic metallic stenting is increasingly used for the management of upper gastrointestinal and left-sided colon obstruction. Whereas stenting for upper gastrointestinal obstruction is always palliative in nature, stenting for colorectal obstruction may be used as a bridge to definitive surgical treatment as well as palliation.

Most stents are placed radiographically in a similar fashion. The site of obstruction is visualized under fluoroscopy with an injection of radiologic contrast. Next, a guidewire is placed across the stricture with either endoscopic or fluoroscopic guidance or both. The self-expandable metal stent is then threaded over the guidewire and across the obstruction, and released into position. Once placed, repeat contrast injection is used to verify position and rule out perforation (120).

Endoscopically or fluoroscopically placed metallic stents have been used selectively for the treatment of malignant gastroduodenal obstructions (121,122 and 123). Gastroduodenal obstructions caused by pancreatic, gastric, and bile duct cancers, as well as lymphoma, have all been treated by metallic stenting (124,125 and 126). Upper gastrointestinal stents have been placed in the esophagus, stomach, duodenum, and across previous surgical anastomoses (124,127,128). Technical success in stent placement is greater than 90% in all series reviewed except one (Table 16-4). After successful stent placement, 85% or more of patients experience clinical improvement and are able to tolerate an oral solid or liquid diet. Major and minor complications related to the placement of the stents are uncommon. However, some stents migrate and obstruct over time. The average stent patency from four series with long-term follow-up was 67 days (121,124,128,129). Stent patency is difficult to determine in this patient population, as many patients expire before stent occlusion. It should be noted that stents are placed in a highly selected patient population and high success rates are due to retrospective analyses without prospective or randomized studies. Still, the stenting of malignant upper gastrointestinal obstructions remains an attractive, simple procedure to relieve vomiting and the inability to eat in selected patients.

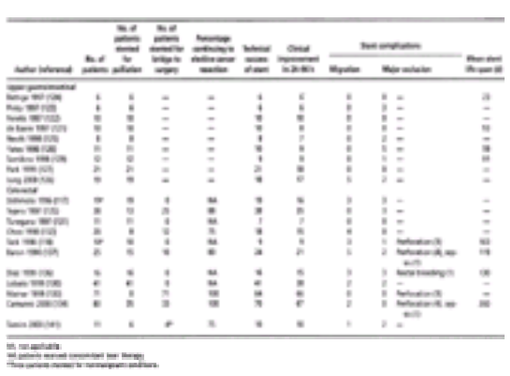


TABLE 16-4. USE OF PALLIATIVE STENTS IN BOWEL OBSTRUCTION

Stenting is more commonly performed for the resolution of malignant colorectal obstruction than upper gastrointestinal obstructions. In this setting, metallic wall stents may be employed for either palliation of obstruction in end-stage patients or as a bridge to further definitive surgical management (130,131 and 132). The use of preoperative stenting allows nonsurgical decompression of the colon and avoids an emergent colostomy. Decompression allows adequate bowel preparation and preoperative optimization. Further, metallic stents have been used after initial laser treatment to maintain colorectal patency (117,118 and 119). Successful placement of stents for either palliation or preoperative decompression is achieved in the vast majority of patients (Table 16-4). Once placed, obstructive symptoms are relieved in 87–100% of cases. Palliative stents are capable of maintaining patency for a mean of 103–200 days. When stents are placed for initial decompression as a bridge to definitive surgery, greater than 85% of patients are able to undergo definitive one- or two-stage surgical resection as evidenced in the three largest studies (133,134 and 135). Minor complications related to the stent placement itself include anorectal pain, bleeding, and tenesmus (117,133,136). Stenting can lead to perforation or sepsis at the time of the procedure itself or by stent migration (134,137). Once in place across the obstruction, stents may eventually migrate or occlude.

MANAGEMENT OF NONMECHANICAL OBSTRUCTION

Patients with malignancy may present with nonmechanical colonic obstruction during their course of disease. Colonic pseudo-obstruction has been managed both pharmacologically and by colonoscopic decompression. A mechanical obstruction must be excluded before the initiation of pharmacological management. Neostigmine has been used effectively to relieve colonic pseudo-obstruction in the nonmalignant setting (138). Further study is warranted to assess the efficiency of neostigmine in pseudo-obstruction associated with malignancy. Use of the prokinetic agent cisapride has also been studied for the treatment of nonmalignant pseudo-obstruction. Cisapride did improve symptoms related to obstruction, but results were similar to a placebo control (139).

Most patients with colonic pseudo-obstruction can be conservatively managed initially with a trial of bed rest, intravenous fluids, and pharmacological therapy. When symptoms worsen or risk of complication increases, colonoscopic decompression is warranted. Perforation from cecal dilatation is the most severe complication of colonic pseudoobstruction. Cecostomy was used in the past to prevent this complication. Successful decompression is now performed with colonoscopy. The majority (68%) of patients are effectively relieved of pseudo-obstruction by colonoscopy (140). If colonoscopy fails, either a right hemicolectomy or cecostomy should be performed for definitive management.

CONCLUSION

Mechanical bowel obstruction in cancer patients is managed initially with intravenous hydration and nasogastric tube placement and correction of electrolyte abnormalities. When possible, mechanical gastroduodenal and colonic obstruction should be treated surgically. Patients with small bowel obstruction should receive a trial of conservative therapy, which may lead to resolution of symptoms. The decision to proceed with surgical intervention in the small bowel ultimately needs to be individualized to each patient.

Palliative management of bowel obstructions, either medical or surgical, is often required in the oncology patient. Medical palliation by administration of a variety of pharmacological agents can control symptoms of nausea, vomiting, pain, and distention in patients who are not surgical candidates. Minimally invasive surgical procedures (e.g., percutaneous endoscopic gastrostomy, laser therapy, and stenting) may palliate symptoms without the need for pharmacological support.

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17

DIAGNOSIS AND MANAGEMENT OF ASCITES

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EPIDEMIOLOGY

Ascites, the accumulation of fluid in the abdomen, is common in patients with certain types of end-stage cancer. Its formation may be a direct result of a malignant process or secondary to unrelated comorbidity. Because the pathophysiology of fluid collection varies, treatment strategies differ. Clinical distinction between the causes of ascites is therefore imperative.

Of all patients with ascites, approximately 80% have cirrhosis (1). Other causes of nonmalignant ascites are accounted for as follows: heart failure, 3%; tuberculosis, 2%; nephrogenic ascites related to hemodialysis, 1%; pancreatic disease, 1%; and miscellaneous entities such as hepatic vein thrombosis (Budd-Chiari syndrome), pericardial disease, and the nephrotic syndrome account for approximately 2% (1). Only 10% of patients who have ascites have a malignancy as the primary cause (1). In these patients, epithelial malignancies, particularly ovarian, endometrial, breast, colon, gastric, and pancreatic carcinomas, cause over 80% of malignant ascites. The remaining 20% are due to malignancies of unknown origin (2). In one study, Runyon has shown that 53.3% of malignant ascites is associated with peritoneal carcinomatosis, 13.3% is associated with massive liver metastases, 13.3% is associated with peritoneal carcinomatosis and massive liver metastases, 13.3% is associated with hepatocellular carcinoma with portal hypertension, and 6.7% is associated with chylous ascites (3).

In general, the presence of ascites portends a poor prognosis, regardless of the cause. Patients with nonmalignant ascites related to cirrhosis have a survival rate of approximately 50% at 2 years (1). The mean survival in patients with malignant ascites is generally less than 4 months (4). However, with ascites due to a malignancy that is relatively sensitive to chemotherapy, such as newly diagnosed ovarian cancer or lymphoma, the mean survival may improve significantly to 32 and 58 weeks, respectively (4).

PATHOPHYSIOLOGY

Nonmalignant Ascites

The mechanisms that lead to the development of ascites are many, and controversy exists regarding which factors are most important. The most common cause of nonmalignant ascites is cirrhosis of the liver. In cirrhotic ascites, abnormal sodium retention is mediated by various hormonal and neural mechanisms, similar to those responsible for excess fluid retention in congestive heart failure. A hemodynamic state exists where total blood volume is increased, cardiac output is increased, and systemic vascular resistance is low. Studies have implicated nitric oxide as one potential mediator of this arterial vasodilation (5). In response, the vasoconstrictors of the renin-angiotensin-aldosterone system and the sympathetic nervous system are activated. Although atrial natriuretic peptide levels are increased, there is reduced renal responsiveness (6). In addition, arginine vasopressin, a potent vasoconstrictor, is activated in a manner independent of the osmotic state (7). The net result is an increase in total body sodium and water. In conjunction with cirrhosis, which has caused increased hepatic venous and lymphatic resistance, severe portal hypertension ensues. The increase in hepatic venous sinusoidal and portal pressures causes the excess fluid volume to localize to the peritoneal cavity secondary to fluid transudation from the splanchnic capillary bed. Ascites accumulation is also exacerbated by diminished intravascular oncotic pressure, resulting from hypoalbuminemia due to decreased synthetic capacity of the cirrhotic liver.

Malignant Ascites

Malignant ascites arises via different pathophysiological mechanisms. In peritoneal carcinomatosis, tumor cells on the peritoneal surface of the abdominal cavity interfere with normal venous and lymphatic drainage, causing fluid to “leak” into the abdominal cavity. In addition to direct tumor involvement of the peritoneal surface, there is also evidence of indirect involvement mediated by humoral factors. Researchers have identified a vascular permeability factor that increases fluid leak from the peritoneal vasculature; vascular endothelial growth factor is a prime candidate for this activity (8). Portal pressures may also be raised by direct tumor invasion of the liver with resultant hepatic venous obstruction. The resultant portal hypertension leads to transudation of fluid across the splanchnic bed into the abdominal cavity. A final mechanism of ascites formation is due to lymphatic obstruction, commonly caused by lymphoma, resulting in chylous ascites.

DIAGNOSIS

History

Patients with ascites commonly notice an increase in abdominal girth, a sensation of fullness or bloating, and early satiety. Other useful historical features include recent weight gain or ankle swelling. Patients may describe vague, generalized abdominal discomfort or a feeling of heaviness with ambulation. They may also note indigestion, nausea, and vomiting due to delayed gastric emptying, esophageal reflux symptoms due to increased intraabdominal pressure, or protrusion of the umbilicus.

Physical Examination

Physical examination for ascites includes inspection for bulging flanks, percussion for flank dullness, a test for shifting dullness, and a test for a fluid wave. Jugular venous distention should also be assessed, as it may indicate a potentially reversible cardiac cause of ascites.

The abdominal flanks bulge when significant ascites is present due to the weight of abdominal free fluid. The examiner should look for bulging flanks when the patient is supine. The distinction between excess adipose tissue and ascites may be made by percussing the flanks to assess for dullness (Fig. 17-1). To detect flank dullness in the supine patient, approximately 1500 ml of fluid must be present (9).

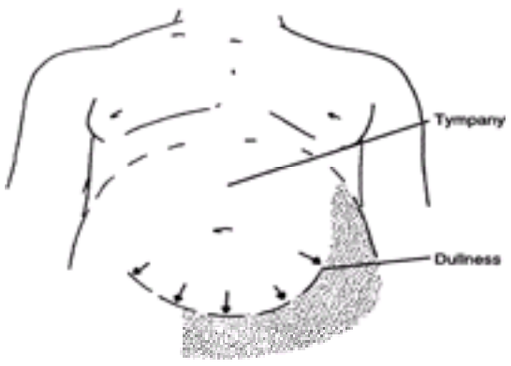

FIGURE 17-1. Shifting dullness.

If dullness to percussion is found, examination for shifting dullness is a useful maneuver. The flank is tapped, and a mark is made on the skin at the location where the tone changes. The patient is then turned partially toward the side that has been percussed. If the location of the dullness shifts upward toward the umbilicus, it is further evidence of intraabdominal ascites (Fig. 17-2).

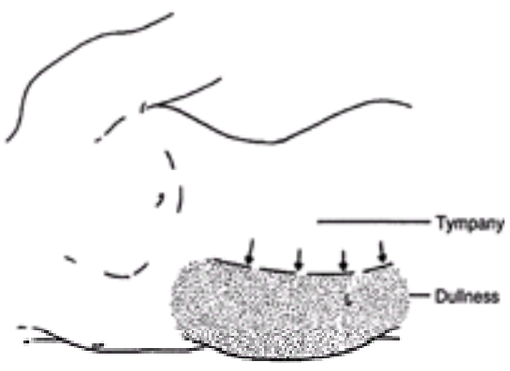

FIGURE 17-2. Tympany and dullness.

The elicitation of a fluid wave may also help to confirm the diagnosis. The test is performed by having an assistant place the medial edges of both hands firmly down the midline of the abdomen to block transmission of a wave through subcutaneous fat. The examiner places his/her hands on the flanks and then taps one flank sharply while simultaneously using the fingertips of the opposite hand to feel for an impulse transmitted through the ascites to the other flank. This test is 90% specific, but only 62% sensitive (10).

Several additional aspects of the physical examination may also be helpful. The liver may be ballotable if it is enlarged and ascites is present. If ascites is severe, the examiner may discern umbilical, abdominal, or inguinal hernias; scrotal or lower extremity edema; or abdominal wall venous engorgement. The umbilicus may be flattened or slightly protuberant. Two additional maneuvers that have been described for the physical diagnosis of ascites, the puddle sign and auscultatory percussion, are not recommended (10).

Several diagnostic tests may be useful, particularly if the physical examination is equivocal. A plain radiograph of the abdomen may demonstrate a hazy or ground-glass pattern. Ultrasonography or computed tomography of the abdomen readily identify as little as 100 ml of free fluid. These latter tests are most helpful in making the diagnosis when there is a relatively small amount of fluid, or when loculation is present.

Laboratory Abnormalities

A diagnostic paracentesis of 10–20 ml of fluid is useful to confirm the presence of ascites. More importantly, it is essential to help determine its cause. Identifying the cause has profound implications for what treatment is attempted.

To perform paracentesis, one of two locations is chosen. The first is a midline location 2 cm inferior to the umbilicus. This location is over the linea alba, which is typically avascular. The second is a location 2 cm superior and medial to the anterior iliac spine and lateral to the edge of the rectus sheath, avoiding entry into the inferior epigastric artery. Ultrasonography may be performed if the fluid is difficult to obtain, loculation is suspected, or surgical scarring is present. Previous surgery in the area of the procedure increases the possibility that the bowel may be adherent to the abdominal wall.

After careful cleansing and local anesthetizing, a 2-inch, 20-gauge angiocatheter is attached to a 20-ml syringe. To minimize the risk of leaking fluid after the procedure, the **Z** technique is performed. The skin is displaced 2 cm relative to the deep fascia. The needle is slowly advanced while a small amount of negative pressure is intermittently applied through the syringe until ascitic fluid is obtained. The intermittent pressure helps to avoid trapping omentum or bowel against the needle tip. After the necessary amount of fluid has been obtained, the needle is withdrawn. The fascial planes overlap to prevent fluid leakage, a common complication with a more direct approach.

The color of the fluid should be noted. A white milky fluid is characteristic of chylous ascites. Bloody fluid is almost always malignant in origin, although it may be due to abdominal tuberculosis. Initial bloody fluid that clears is more likely related to the trauma of the procedure.

The fluid should undergo cytologic analysis and determinations of cell count with differential and total protein concentrations. A Gram's stain with culture should be performed if infection is suspected. Inoculation of ascites directly into blood culture bottles increases the sensitivity of detecting infection up to 85% (11). Cytology is the most specific test to demonstrate that the ascites is due to malignancy. Cytology is approximately 97% sensitive with peritoneal carcinomatosis (3), but is not helpful in the detection of other types of malignant ascites. Therefore, the absence of malignant cells does not exclude malignancy as a cause. The cell count, particularly the absolute neutrophil count, is useful in the presumptive diagnosis of bacterial peritonitis. If the neutrophil count is greater than 250 cells/ml, bacterial peritonitis is presumed.

The total protein concentration has been used to classify ascites into the broad categories of exudate (total protein >25 g/l) or transudate (total protein <25 g/l). However, this classification system has limitations and sometimes fails to lead to optimal treatment. It has been superseded by the serum-ascites albumin gradient (SAAG). It is defined as the serum albumin concentration minus the ascitic fluid albumin concentration. The SAAG directly correlates with portal pressure (12). Patients with a SAAG of 1.1 g/dl or more have ascites that is due in part to increased portal pressures, with an accuracy of 97%. Patients with a SAAG less than 1.1 g/dl do not have portal hypertension, with an accuracy of 97% (13).

The superiority of the SAAG to the exudate/transudate characterization is shown by two examples. Cardiac ascites is associated with portal hypertension and would be expected to be transudative; however, the total protein levels in cardiac ascites are often exudative (13,14). Furthermore, ascites associated with spontaneous bacterial peritonitis (SBP) would be expected to be exudative consistent with an infection. However, SBP almost exclusively develops in low protein content ascites associated with portal hypertension, and total protein levels are typically in the transudative range (13).

MANAGEMENT

Overall goals for patient care should be considered before specific choices for managing ascites are made. The prognosis, expected response to management of the underlying conditions, and preferences for treatment should be established with the patient and family before any treatment plan is instituted. Each ascites treatment modality has associated burdens and benefits that deserve to be considered and discussed.

The discernment of the ascites as having a low or high SAAG is critical in determining the overall management plan. Ascites due to portal hypertension *is* in equilibrium with total body fluid. The most common cause of nonmalignant ascites, cirrhosis, falls within this category. Efforts to restrict salt and to affect fluid balance with diuretics are often successful. Malignant ascites may or may not be responsive to these efforts, depending on its cause. In peritoneal carcinomatosis and chylous ascites, the SAAG is low, there is no portal hypertension, and the ascites *is not* in equilibrium with total body fluid (15). Consequently, salt and fluid restriction and diuretics may be of little use. Their injudicious use may result in intravascular volume depletion, diminished renal perfusion, azotemia, hypotension, and fatigue (2). There are forms of malignant ascites with a high SAAG. For example, in cases of massive hepatic metastasis, portal hypertension is present. The resulting malignant ascites is responsive to salt restriction and diuretics (15). One exception to this rule is nephrotic syndrome in which the SAAG is low but the ascites is diuretic responsive (16). See Table 17-1 for a summary.

Cause of ascites	Serum-ascites albumin gradient	Typical diuretic response
Cirrhosis	High (≥1.1 g/dl)	Yes
Alcoholic hepatitis	High (≥1.1 g/dl)	Yes
Cardiac ascites	High (≥1.1 g/dl)	Yes
Fulminant hepatic failure	High (≥1.1 g/dl)	Yes
Budd-Chiari syndrome	High (≥1.1 g/dl)	Yes
Portal vein thrombosis	High (≥1.1 g/dl)	Yes
Veno-occlusive disease	High (≥1.1 g/dl)	Yes
Acute fatty liver of pregnancy	High (≥1.1 g/dl)	Yes
Myxedema	High (≥1.1 g/dl)	Yes
Tuberculosis (without cirrhosis)	Low (≤1.1 g/dl)	No
Pancreatic ascites (without cirrhosis)	Low (≤1.1 g/dl)	No
Biliary ascites (without cirrhosis)	Low (≤1.1 g/dl)	No
Nephrotic syndrome	Low (≤1.1 g/dl)	Yes
Serositis from connective tissue disease	Low (≤1.1 g/dl)	No
Bowel obstruction/infarction	Low (≤1.1 g/dl)	No
Mixed ascites (i.e., cirrhosis plus infection or cancer)	High (≥1.1 g/dl)	Yes
Peritoneal carcinomatosis	Low (≤1.1 g/dl)	No
Massive hepatic metastasis	High (≥1.1 g/dl)	Yes

TABLE 17-1. CAUSES OF ASCITES AND DIURETIC RESPONSIVENESS

Interventions for ascites management in the supportive or palliative care setting should generally be reserved for patients who are symptomatic. The following symptoms may spur the need for intervention when the ascites seems to be responsible for or contributing to

- Dyspnea
- Fatigue
- Anorexia or early satiety
- Nausea/vomiting
- Pain
- Diminished exercise tolerance

Dietary Management

The dietary management of ascites with a high SAAG begins with sodium restriction. Patients with cirrhosis may excrete as little as 5–10 mEq of sodium per day in their urine. Limiting sodium intake to 88 mmol or 2 g/day (equivalent to 5 g of sodium chloride per day) is an attainable goal for a motivated patient but does make food less palatable. Considering a patient's goals of care, it may be better to liberalize the sodium intake and control ascites through other methods.

Patients are also prone to develop dilutional hyponatremia. The management of this condition has typically been fluid restriction to 1 l/day. In the patient with advanced disease, when treatment goals are purely palliative, fluid restriction is usually intolerably burdensome. Judicious medical management may be less burdensome. For patients with cirrhotic ascites, serum sodium levels as low as 120 mmol/l are well tolerated and rarely dictate intervention (1).

Medical Management

For the majority of patients, the medical management of ascites is palliative. That is, the goal of therapy is to minimize symptoms and optimize quality of life without the expectation that the underlying cause can be reversed. *Systemic chemotherapy* may be an effective management strategy for patients with ascites due to a responsive malignancy (e.g., lymphoma, breast, or ovarian cancer). In addition to systemic chemotherapy, intraperitoneal treatment with chemotherapeutic and biological agents is being pursued. Intraperitoneal chemotherapy can deliver high doses to peritoneal sites with minimal systemic side effects. Phase III trials have been performed with ovarian and colon cancer. Alberts et al. showed that, in conjunction with intravenous cyclophosphamide, intraperitoneal cisplatin versus intravenous cisplatin significantly increased survival, to 49 months from 41 months (17). Vaillant et al. showed that a short period of intraperitoneal 5-fluorouracil after surgery for colon cancer decreased recurrence for stage II but not stage III (18). Biologically active agents have also been used intraperitoneally to treat malignant ascites. These include interferon (IFN)-a, IFN-b, IFN-g, tumor necrosis factor, and interleukin-2 (19). Early clinical trials have yielded mixed results. For example, tumor necrosis factor-a has yielded conflicting results with malignant ascites (20,21). To date, no phase III clinical trials have been performed. Thus, the overall efficacy and role of intraperitoneal chemotherapeutic and biological agents in both curative and palliative care remains to be determined.

Diuretic therapy is useful for some patients, particularly those whose ascites has a high SAAG. As with any drug therapy in the supportive care setting, the patient's symptoms should first be ascertained and the benefit versus the burden of therapy considered. The goal of diuretic therapy is to reduce extravascular fluid accumulation. Diuretic therapy should be directed to achieve a slow and gradual diuresis that does not exceed the capacity for mobilization of ascitic fluid. In the patient with ascites and edema, edema acts as a fluid reservoir to buffer the effects of a rapid contraction of plasma volume. Approximately 1 l/day (net) can safely be diuresed. In patients with ascites but without edema, diuresis may be achieved at the expense of the intravascular volume, leading to symptomatic orthostatic hypotension. In these patients, a more modest goal is to achieve net diuresis of 500 ml/day. Diuretics should not be administered with the goal to render the patient free of edema and ascites. Rather, only enough fluid should be mobilized to promote the patient's comfort. Overly aggressive diuretic therapy for ascites in a patient with nonmalignant ascites due to cirrhosis has been associated with the hepatorenal syndrome and death (22). There are no reports of hepatorenal syndrome associated with paracentesis for malignant ascites.

In patients with ascites for whom diuretics may be helpful, the renin-angiotensin-aldosterone system is activated. Therefore, the initial diuretic of choice for management is one that acts at the distal nephron to block the effect of increased aldosterone activity (23,24). Spironolactone, beginning with 100 mg/day and titrated up to effect or 400 mg/day, is often a useful agent with which to begin (Table 17-2). Given the long half-life of spironolactone, daily dosing is all that is needed. Spironolactone may cause painful gynecomastia (25). Amiloride hydrochloride, 10 mg/day, is an alternative. It is faster acting and does not cause gynecomastia. It can be titrated up to a dose of 40 mg/day. Because these diuretics are relatively potassium sparing, patients should be advised not to use salt substitutes, as these are usually preparations of potassium chloride. If patients have a suboptimal response despite maximal use of the distal diuretics, a loop diuretic may be added, beginning at low doses (e.g., furosemide, 40 mg orally daily). There is evidence to support the combined use of a distal tubule diuretic and a loop diuretic at the beginning of therapy (24). This combination may effect a more rapid diuresis while maintaining potassium homeostasis. A ratio of 100 mg of spironolactone to 40 mg of furosemide is recommended as a starting point (1). The ratio can be adjusted to maintain normokalemia. The dosages can be increased in parallel until the goals of therapy have been attained, up to a maximum of spironolactone, 400 mg/day, and furosemide, 160 mg/day, or until therapy is limited by side effects (1). If there is no response to this level of therapy, the ascites is considered refractory to diuretic therapy if the following are true: (a) salt intake is appropriately limited, and (b) nonsteroidal anti-inflammatory medications, which can affect glomerular filtration, are not being used.

Diuretic	Major site of action	Dosage range	Comments
Spironolactone	Distal tubule	100–400 mg/d	Long half-life; gynecomastia
Amiloride hydrochloride	Distal tubule	5–40 mg/d	–
Triamterene	Distal tubule	100–300 mg/d	–
Furosemide	Loop of Henle	40–160 mg/d	–
Ethacrynic acid	Loop of Henle	50–200 mg/d	Can be used for sulfa allergy

TABLE 17-2. DIURETICS

In the patient who has limited mobility, urinary tract outflow symptoms such as hesitancy and frequency, poor appetite, and poor oral intake, or who has difficulties related to polypharmacy, diuretic therapy may be excessively burdensome. Injudicious diuretic therapy can result in incontinence (with attendant self-esteem and skin care issues), sleep deprivation from frequent urination, fatigue from hyponatremia or hypokalemia, and falls from postural hypotension.

Patients with cirrhotic ascites with low protein content are at increased risk of SBP (26). This increased risk may be due to decreased opsonin levels in the ascites (27). Patients with SBP may be asymptomatic or may note fever, abdominal pain, nausea/vomiting, or mental status changes. Studies have indicated that antibiotic prophylaxis is effective in preventing SBP. Norfloxacin, 400 mg/day, ciprofloxacin, 750 mg/week, or one trimethoprim and sulfamethoxazole (Septra DS)/day Monday through Friday as primary prophylaxis significantly decrease the risk of developing SBP (28,29,30). Liver transplant protocols call for the routine use of SBP prophylaxis (31). Prophylaxis raises the concern of drug-resistant organisms. The long-term clinical significance remains unknown, but after 6 months on once a week ciprofloxacin there was no evidence of resistance (29). The use of prophylaxis in an individual case is dependent on the overall treatment goals and the disease context.

Therapeutic Paracentesis

Large-volume therapeutic paracentesis (³5 liters) with concurrent colloid infusion is a simple procedure and is associated with minimal morbidity or mortality (32,33). The symptom response is much faster than when diuretics are used alone. In the patient with refractory ascites it may be the only therapeutic modality that is effective. In fact, total paracentesis (mean, 10.7 liters) associated with colloid infusion has been shown to be safe (34). If the ascites is in equilibrium with the systemic circulation, as is the case with portal hypertension, there is a risk of hemodynamic compromise. Colloid plasma volume expansion (e.g., 6–8 g of albumin per liter of ascites removed) has been used to avoid this complication, but its use remains controversial. Ginès et al. (33) performed large-volume paracentesis with and without albumin. They demonstrated that without albumin, they could measure increases in blood urea nitrogen, plasma renin, and aldosterone, and decreases in plasma sodium, which were avoided by the infusion of intravenous albumin. Antillon and Runyon (35) argue that these laboratory value changes are asymptomatic and do not necessarily indicate increased morbidity or mortality. Kao et al. performed large-volume paracentesis (5 liters) on diureticresistant patients with tense ascites without the infusion of albumin and noted no significant hemodynamic compromise (36). Runyon argues that the discrepancy may be due to patient population differences. Further studies may elucidate under what circumstances colloid is and is not indicated. Although albumin is expensive, it is not known to cause harm. Practitioners may opt to use colloid for large-volume paracentesis until more definitive guidelines exist for ascites due to portal hypertension.

Surgical Procedures

Liver transplantation offers cure for a subset of patients with cirrhosis (31) and a subset of patients with small hepatocellular carcinoma (37).

Other surgical techniques offer palliation. Peritoneovenous shunts have been reported for management of malignant and nonmalignant ascites. They are placed surgically during a 30- to 60-minute procedure while the patient is under local anesthesia. Their purpose is to drain ascites from the peritoneal space via a one-way valve into the thoracic venous system. Unfortunately, the rate of complications is high, including shunt occlusion, heart failure due to fluid overload, infection, and disseminated intravascular coagulation. Stanley et al. (38) and Gines et al. (39) studied serial paracentesis compared with peritoneovenous shunts in patients with cirrhosis. There was no survival improvement and a high rate of complications with the peritoneovenous shunts. Similarly, Gough and Balderson (40) compared peritoneovenous shunts with nonoperative management in patients with malignant ascites. They found no difference in survival or quality of life. Thus, although there may be specific cases in which peritoneovenous shunting is advantageous in either nonmalignant or malignant ascites, serial paracentesis remains the first-line therapy.

Externally draining, implanted abdominal catheters may be beneficial for selected patients who require repeated large-volume paracentesis for comfort and whose prognosis warrants a surgical procedure. The catheter is surgically placed in the peritoneal cavity with an external drain, which can be accessed intermittently by physicians, nurses, or even trained family members (41). There are no comparative studies between these implanted catheters and serial paracentesis in patients with cirrhotic or malignant ascites. A study of 17 patients with an implanted catheter and abdominal carcinoma was complicated by two cases of cellulitis, one case of peritonitis, and eight cases of asymptomatic culture-positive ascites (42). With no guidance from the literature, use of implanted catheters must be individualized.

The transjugular intrahepatic portosystemic shunt (TIPS) is a procedure performed by interventional radiologists that creates a side-to-side shunt that effectively relieves portal hypertension. For patients with cirrhosis and refractory ascites with relatively good hepatic and renal function, TIPS is considered the treatment of choice. Rossle et al. showed that in comparison to serial large-volume paracentesis, TIPS led to a higher rate of ascites resolution and improved survival without transplantation and without an increase in the risk of hepatic encephalopathy (43). There was, however, almost a 40% rate of shunt malfunction. TIPS has also been employed in a few cases of malignant ascites associated with portal hypertension. In two cases of malignant portal and hepatic vein occlusion, TIPS improved ascites and quality of life (44). Whether to pursue any of the above invasive surgical procedures is dependent on the patient's goals and the disease context.

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18

HICCUPS AND OTHER GASTROINTESTINAL SYMPTOMS

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To eat is human, to digest is divine. (Mark Twain)

Gastrointestinal (GI) symptoms are commonly seen in cancer patients, regardless of the disease site. These symptoms are experienced during the course of the illness or as a result of therapy. However, it should be remembered that many GI problems seen in cancer patients are also seen in those without cancer. In fact, some GI symptoms are very common, and although they do cause distress, they rarely represent life-threatening pathology. This presents a problem, as patients and physicians face the concern that every new symptom is related to the cancer. This chapter focuses primarily on GI symptoms as they relate to cancer and its treatment, but the reader is reminded that most GI symptoms are not directly due to the cancer.

HICCUPS

Definition/Incidence

Hiccup is a spasmodic, involuntary contraction of the inspiratory (external) intercostal muscles and the diaphragm associated with a strong, sudden inspiration and abrupt glottic closure. The inspiratory effort does not result in lung volume changes and there are minimal ventilatory effects (1,2).

Pathophysiology/Etiology

Hiccup is a primitive reflex that, unlike cough or gagging, has no known purpose. The reflex arch contains three parts. The afferent portion consists of branches of the vagus nerve, the phrenic nerve, and the sympathetic chain from T-6 to T-12. The central connection, or “hiccup center,” is located in the spinal cord between C-3 and C-5. The efferent limb is primarily the phrenic nerve with involvement of the efferents to the glottis and accessory muscles of respiration (3). Hiccups result from unilateral (usually left) or bilateral contraction of the diaphragm (one side is dominant)(4).

In addition to the neural pathways, numerous anatomical structures are involved in the mechanism of hiccup (epiglottis, larynx, hyoid muscles, superior constrictor of the pharynx, esophagus, stomach, diaphragm, and exterior intercostal, sternocleidomastoid, anterior serratis, and scalene muscles). Given this extensive list, it is not surprising that hiccup has been associated with many conditions affecting the central nervous system (CNS), thorax, mediastinum, and abdominal viscera, although a cause-and-effect relationship has not always been clear. One report listed over 100 causes, the most common being an overdistended stomach (5). Other common causes of hiccup include esophagogastric irritation, ileus, peridiaphragmatic irritation, general anesthesia, surgery, and excessive alcohol intake. Some cancer-related causes of persistent and intractable hiccup are listed in Table 18-1.

Intracranial neoplasms
Uremia
Alcohol
Hyponatremia, hypokalemia, hypocalcemia
Fever
Diaphragmatic irritation (diaphragmatic tumors, pericarditis)
Pleuritis
Esophageal obstruction
Pericarditis
Hepatomegaly
Subphrenic abscess
Esophageal cancer
Mediastinal tumors
Herpes zoster
Lung cancer
Gastric distention
Gastric cancer
Pancreatic cancer
Intraabdominal abscess
Bowel obstruction
Gastrointestinal hemorrhage
Short-acting barbiturates
Dexamethasone
Diazepam, chlordiazepoxide
Infection (meningitis)
Grief reaction
Psychosis

[a]A comprehensive list of the causes of hiccups can be found in Launois S, Bizec JL, Whitelaw WA, et al. Hiccups in adults: an overview. Eur Respir J 1993;6:563s–57s.

TABLE 18-1. CAUSES OF HICCUPS IN THE CANCER PATIENT[a]

Treatment/Management

Remedies for hiccup are numerous (6), although no single maneuver or medication is consistently effective. Management is usually aimed at inhibiting or interrupting the irritated reflex arc. Many folk remedies are variants of the Valsalva maneuver (expiring forcefully against a closed glottis). Presumably this inhibits an excitatory impulse to the diaphragm and intercostal muscles. Simple strategies include ocular compression, carotid sinus massage, traction on the tongue, ice water gargles, noxious odors or tastes, breath holding, rebreathing into a paper bag, gagging, drinking from a glass while holding a pencil between the teeth or while bending over head down, taking as many sips of fluid as rapidly as possible without breathing, ingesting granulated sugar, or inducing emesis. Although these measures have not been subjected to controlled clinical trials, most are worth a try. However, many are not practical for the oncology population, which may be too debilitated to tolerate even simple maneuvers (e.g., breath holding), much less dangerous ones (e.g., carotid massage). Many drugs have been advocated for the management of hiccups. The drugs most frequently used are prokinetic agents, such as metoclopramide (7), and sedatives, including most (if not all) of the benzodiazepines. The phenothiazine drugs are also widely used, most commonly chlorpromazine (8). Use of the anticonvulsants diphenylhydantoin (9), carbamazepine (10), and valproic acid (11) has been reported. Efficacy has been claimed for a variety of drugs that principally have a peripheral action [e.g., atropine sulfate (and other anticholinergic agents), edrophonium chloride, procainamide hydrochloride, and quinidine sulfate]. Amitriptyline hydrochloride (12) and methylphenidate hydrochloride (13) have been used, as well as the calcium channel blocker nifedipine (14) and the antispasticity agent baclofen (15), which acts on the spinal cord. Some of these seem to work some of the time, but none work consistently.

Various invasive methods have been tried. Gastric aspiration may be useful if overdistention of the stomach is a cause of hiccup. The insertion of a nasogastric tube may also serve a purpose by stimulating the pharynx or causing gagging (16). High-pressure oxygen inhalation has been tried. Percutaneous stimulation of the phrenic nerve has also been reported (17). A surgical approach consists of an attack on the phrenic nerve (by a crush technique), usually first attempted on the left. Regardless of treatment, in most cases, hiccups stop because of, or in spite of, therapeutic measures.

Clearly, many medications have been tried in the search for an effective treatment. However, a few drugs appear to be more effective than the rest (Table 18-2). Because gastric distention is the most common cause of hiccups in cancer, a treatment plan directed at decompression of the stomach should be the first intervention unless another cause can be clearly identified. Over-the-counter agents, including antacid and antiflatulence preparations, may provide relief. Chlorpromazine is advocated most frequently, but the side effects of hypotension and sedation make it less attractive in the oncology population. Haloperidol may be a better choice for those taking opioids (18).

Drug	Dose	Side effects
Metoclopramide	10 mg i.v. 10 mg p.o. 3-4 times daily	Extrapyramidal symptoms[a]
Chlorpromazine	25–50 mg i.v. infused slowly 25–50 mg p.o. 3 times daily	Sedation, hypotension
Haloperidol	1–5 mg p.o. 1–4 mg p.o. 3 times daily	Sedation, extrapyramidal symptoms
Baclofen	5 mg p.o. 15 mg every 3 days to max 60 mg	Sedation, confusion; less commonly, nausea and fatigue
Nifedipine	10 mg p.o. 3 times daily 10–20 mg p.o. 3 times daily	Hypotension, use with caution in patients with coronary artery disease

[a]More common in younger women.

TABLE 18-2. COMMONLY USED DRUGS IN THE TREATMENT OF HICCUPS

It is important to remember that hiccup in the cancer patient may be more than just an annoyance or signal pathology; it may exacerbate an already fragile condition by interfering with food intake, causing insomnia or exacerbating pain and other symptoms (19,20). For this reason, it may be advisable to pursue diagnosis and treatment more aggressively than in the general population.

DYSPEPSIA

Definition/Incidence

It has been said that dyspepsia defies definition. In 90 hospitalized patients asked to define indigestion, most linked it with psychological factors, feeding patterns, and bowel function, rather than physical illness (21). The international working party defines dyspepsia as episodic or persistent symptoms that include abdominal pain or discomfort, postprandial fullness, abdominal bloating, belching, early satiety, anorexia, nausea, vomiting, heartburn, and regurgitation. There is considerable overlap between this constellation of symptoms and those of gastroesophageal reflux disease (GERD), biliary tract disease, irritable bowel syndrome, and chronic pancreatitis. Dyspepsia is a recurrent problem, occurring more than six times per year in 6% of the population (22).

Pathophysiology/Etiology

Results of upper GI endoscopy in 3667 general medical patients with dyspepsia were as follows: normal (34%), gastroesophageal reflux (24%), inflammation (21%), ulcer (20%), and cancer (2%)(22). Dyspepsia is divided into two categories: organic dyspepsia and nonulcer dyspepsia. Patients in the first group have anatomical abnormalities definable by routine investigation (peptic ulcer disease and gastric cancer account for almost all cases). Patients in the second category have symptoms for which no focal lesion or systemic disease can be found. These patients can be placed in subcategories (Table 18-3) on the basis of their symptoms. However, the subcategories are not mutually exclusive; many of these patients have overlapping symptoms.

Classification	Symptoms	Treatment
Reflux-like	Heartburn, regurgitation without esophagitis	Antacid, H_2 blocker, proton pump inhibitor
Ulcer-like	Epigastric pain relieved by food and antacids, relapse and remission, without ulcer	Same
Dysmotility-like	Abdominal bloating, distention, early satiety, nausea, vomiting	Prokinetic agent, antiflatulence agent
Nonspecific	Symptoms do not fall into one of the three categories above	Start simple: antacid, antiflatulence agent (simethicone)

TABLE 18-3. CLASSIFICATION OF NONULCER DYSPEPSIA BY SYMPTOM TYPE AND THEIR TREATMENTS

Causes of dyspepsia in cancer include gastric cancer or lymphoma, gastritis secondary to radiotherapy/chemotherapy, gastric compression secondary to intraabdominal tumor, hepatomegaly, splenomegaly, ascites, gastric outlet obstruction due to tumor, or gastroparesis secondary to anticholinergic drugs, opioids, or autonomic nervous system dysfunction.

Management/Treatment

The management of dyspepsia should be directed at the cause, if organic. Treatment may be based on previous history (e.g., obstructing lesion responding to primary tumor treatment) or recent endoscopy findings. In nonulcer dyspepsia, treatment should be based on symptoms (Table 18-3).

PYROSIS

Definition/Incidence

Pyrosis is probably the most common GI complaint in the Western population. Surveys reveal that 33–44% complain of heartburn at least monthly and that 7–13% may have daily symptoms (23). Pyrosis is a retrosternal burning sensation that usually radiates proximally from the xiphoid process to the neck. It is caused by reflux of the gastric contents into the esophagus and is often precipitated by lying down or bending over, particularly after the ingestion of certain foods or large meals. Uncomplicated heartburn is usually relieved by antacids. The chronic or relapsing condition, GERD, can be a difficult problem to control, resulting in reflux esophagitis. Although there is no clear evidence that GERD is more common in those with cancer, certain conditions in this population may increase their risk, such as intraabdominal lesions, which increase pressure on the stomach.

Pathophysiology/Etiology

Several mechanisms are responsible for gastroesophageal reflex. The majority of episodes are due to transient relaxations of the lower esophageal sphincter (LES). Other factors that may contribute to GERD include transient increases in intraabdominal pressure, impaired clearance of acid from the esophagus because of diminished or absent peristalsis, and impaired salivary acid-neutralizing capacity.

The physiological mechanisms that produce heartburn are poorly understood. Although the reflux of gastric acid is most commonly associated with heartburn, the same symptom may be elicited by esophageal balloon distention. The correlation of discrete episodes of acid reflux and symptoms is poor. For example, postprandial gastroesophageal reflux is common in healthy people, but symptoms are rare. Symptoms must require more than esophageal contact with acid. Mucosal disruption with inflammation may be a contributory factor, but on endoscopy, the esophagus usually appears normal.

A number of foods, drugs, and neurohumoral factors reduce basal LES pressure, making patients prone to gastroesophageal reflux and heartburn (Table 18-4). Avoidance of these foods and medications often constitutes the initial treatment of GERD. Some common agents that increase the LES include a protein meal, bethanechol chloride, metoclopramide, and a-adrenergic agonists.

Low LES pressure	Direct mucosal irritant	Increased intraabdominal pressure	Others
Certain foods	Certain foods	Bending over	Supine position
Fats	Citrus products	Lifting	Lying on right side
Sugars	Tomato-based products	Straining at stool	Red wine
Chocolate	Spicy foods	Exercise	Emotions
Onions	Coffee		
Coffee	Medications		
Alcohol	Aspirin		
Cigarettes	Nonsteroidal anti-inflammatories		
Medications	Tetracycline		
Progesterone	Quinidine sulfate		
Theophylline	Potassium chloride tablets		
Anticholinergic agents	Iron salts		
Adrenergic agonists			
Adrenergic antagonists			
Diazepam			
Estrogens			
Mint, anise, dill			
Benzodiazepines			
Meperidine hydrochloride			
Nitrates			
Calcium channel blockers			

LES, lower esophageal sphincter.

TABLE 18-4. AGGRAVATING FACTORS FOR HEARTBURN

Many disorders cause epigastric or substernal pain similar to heartburn, making it important to determine the cause in each patient. Causes include collagen-vascular disorders, scleroderma, mixed connective tissue disorders, raised intraabdominal pressure, gastroparesis, nasogastric tube, prolonged recumbent position, persistent vomiting, pregnancy, hypothyroidism, Zollinger-Ellison syndrome, medications, and some surgical procedures (e.g., myotomy, esophagogastrectomy).

Heartburn is most frequently noted within 1 hour after eating, particularly after the largest meal of the day. Wine drinkers may have heartburn after hearty red wines but not after white wines. Lying down, especially after a late meal, causes heartburn within 1–2 hours; in contrast to peptic ulcer disease, heartburn does not awaken the person in the early morning. Heartburn may be accompanied by regurgitation, a bitter acidic fluid in the mouth that is common at night or when the patient bends over. The regurgitated material comes from the stomach and is yellow or green, which suggests the presence of bile. It is important to distinguish regurgitation from vomiting. The absence of nausea, retching, and abdominal contractions suggests regurgitation rather than vomiting. Furthermore, the regurgitation of bland material is atypical for acid reflux disease and suggests the presence of an esophageal motility disorder (i.e., achalasia) or delayed gastric emptying.

Treatment/Management

Initial treatment includes avoiding precipitating factors when possible, sleeping with head elevated, weight reduction (if feasible), and antacids. More aggressive therapy includes H_2 receptor blockers, sucralfate, or omeprazole (initial doses as for peptic ulcer; in unresponsive cases, higher than standard doses of H_2 receptor blockers may be effective). Agents that increase LES pressure and enhance gastric emptying may be helpful, such as metoclopramide. Long-term therapy is usually necessary.

EARLY SATIETY

Definition/Incidence

Early satiety is the desire to eat combined with an inability to consume more than an unusually small amount of food. This is in contrast to anorexia, in which there is a reduced desire to eat. Early satiety should be distinguished not only from anorexia, but also from nausea, bloating, postprandial filling, pyrosis, food aversion, and dyspepsia. However, all of these symptoms may be due to the same physiologic abnormality—delayed gastric emptying. Patients generally do not report this symptom unless questioned. The incidence of cancer-related early satiety varies from 13–62% depending on the study and population being evaluated (24,25,26 and 27).

Pathophysiology/Etiology

Satiety results from overlapping stimuli from the CNS and GI tract that affect food intake. The nutrients ingested and peptide hormones (insulin, glucagon, norepinephrinestimulating a_2-adrenergic receptors in the medial hypothalamus), along with serotonin and dopaminergic-/a-adrenergic receptors in the lateral hypothalamus, all affect satiety. Cholecystokinin may have primary effects on satiety. Exogenous administration of peptides like cholecystokinin and bombesin affect satiety both centrally and peripherally and inhibit feeding activity in animals.

Early satiety may be due to tumor encroachment on the GI tract, inappropriate satiety signals from oropharyngeal receptors, hyperglycemia, or gastric muscle atrophy. Another important cause appears to be reduced upper GI motility due to autonomic nervous system dysfunction, possibly a paraneoplastic syndrome (28). Tumor type and previous chemotherapy treatment have not been shown to affect the incidence of early satiety in cancer. However, those with taste aversions appear to have a higher incidence of early satiety than those without (29).

Treatment/Management

It is important to determine that early satiety is the reported symptom. If bloating, pyrosis, anorexia, or nausea not due to gastric status is present, it should be treated appropriately. If there is pressure on the stomach (“squashed stomach”), it should be reduced if possible, although in many cases it is not. Problems such as ascites may be amenable to paracentesis, which can provide temporary relief. Those with gastroduodenal ulcers should be treated with appropriate therapy (H_2 blocker, proton pump inhibitor, antibiotic). In patients with cicatrization at the pyloric outlet, balloon dilatation may afford relief for variable periods.

Patients with early satiety should be instructed to eat frequent, small meals, with the bulk of their daily intake consumed early, as gastric stasis increases as the day progresses. They should also be instructed to eat sitting up and avoid liquids at mealtimes, as this promotes gastric distention and the sense of fullness. Prokinetic agents (e.g., metoclopramide, domperidone) may be of particular value. The rationale for prokinetic agents in early satiety is based on the assumption that the symptom is due to delayed gastric emptying. Metoclopramide is the drug of choice in the United States (30). It is a dopamine antagonist that increases LES pressure

and enhances gastric antral contractility. It is generally well-tolerated orally, but extrapyramidal reactions, which appear to be more common in young women, do occur; insomnia (often noted to be “jumpy legs” on further questioning) and sedation have also been reported. Metoclopramide, 10 mg three times daily orally, is effective treatment for many and enhances food intake. The central effects of metoclopramide may have a direct effect on anorexia to improve appetite in addition to the peripheral effects on gastric contractility. The other prokinetic agents, cisapride and domperidone, are not available in the United States. Cisapride has been removed from the market due to drug interactions causing cardiac abnormalities. Domperidone, also a dopamine antagonist, does not cross the blood–brain barrier, hence its side effect profile is superior to metoclopramide; unfortunately, it has not yet been approved in the United States. Erythromycin is another prokinetic agent but is less useful in cancer-related gastroparesis as it causes gastric dumping, which is useful in acute gastric stasis (e.g., diabetic gastroparesis).

GASTROINTESTINAL HEMORRHAGE

Definition/Incidence

GI bleeding may originate at any site from the mouth to the anus. It can be occult or overt, with varying degrees of severity. A careful history and physical examination often suggest the site as well as the cause of the bleeding. Although controversial, most agree that 20% loss of circulating volume produces hemodynamic changes and greater than 30% produces shock with organ damage. In the debilitated cancer patient, the ability to tolerate a GI hemorrhage is compromised and the signs and symptoms may occur with far less blood loss.

The overall incidence of acute upper GI hemorrhage is 100 hospitalizations per 100,000 adults per year (31). In a study of over 15 million people there was an overall mortality rate of 14% (32). However, in patients younger than 60 years of age without malignancy or organ failure, the mortality was only 0.6%. In 800 admissions to a palliative home care program, the incidence of GI bleeding was 2.3%; those with liver cancer or hepatic metastases were at higher risk (33).

Pathophysiology/Etiology

GI bleeding can be multifactorial, and one should not assume that the tumor is the source of bleeding. In a general population of 2225 patients, duodenal ulcer (24%), gastric erosions (23%), and gastric ulcer (21%) accounted for the majority of the upper GI bleeding (34). In cancer, gastritis (36%), peptic or stress ulceration (26%), and tumor necrosis (23%) are the most common causes. Candida esophagitis, particularly during chemotherapy administration, Mallory-Weiss mucosal tears with significant bleeding in the setting of thrombocytopenia (35), and inflammatory conditions (e.g., radiation therapy) are less common (36). In the general population, 43% of lower GI bleeding is due to diverticulosis (37). Massive lower GI bleeding can be a late complication of the high-dose radiation therapy used for treatment of GI, gynecologic, or genitourinary cancer.

Other causes of bleeding in the cancer patient include thrombocytopenia and coagulopathies secondary to the disease or the treatment. Aggressive chemotherapy may cause stress-related ulceration of the mucosa or suppress bone marrow production. The incidence of GI perforation after chemotherapy is 10%; most are lymphoma patients. GI lymphomas are more common sources of tumor bleeding than other intraabdominal malignancies. Bleeding is the presenting symptom in 15–28% of patients, but only 3–4% have perforation (38). Hemorrhage has been reported in 27% of those receiving chemotherapy for unresected lymphoma. Resection before treatment may reduce the bleeding and perforation by 50%. Cytosine arabinoside can cause bowel necrosis, and hepatic arterial infusion of fluorodeoxyuridine may cause upper GI toxicity, resulting in gastritis and peptic ulcers. The initiation of chemotherapy has been reported to trigger or accelerate disseminated intravascular coagulation in lymphoma, presumably due to release of thromboplastin-like or other clot-promoting materials (39).

Medications may be responsible for GI bleeding. Drugs usually implicated are corticosteroids, nonsteroidal antiinflammatory drugs, and aspirin (40). Cephalosporins, streptomycin, isoniazid, penicillin, b-lactam, and amphotericin B may cause bleeding due to clotting factor inhibitors or impairing of platelet function.

Upper Gastrointestinal Bleeding—Diagnostic Evaluation

Hematemesis is the vomiting of blood, either bright red or dark, with a “coffee grounds” appearance. Melena is foul smelling stool with a coal black, sticky, tar-like appearance. Hematemesis and melena locates the source of bleeding as the nasopharynx, esophagus, stomach, duodenum, or, rarely, the proximal jejunum. Endoscopy is used to evaluate upper GI bleeding. Hemodynamically unstable patients should undergo emergent endoscopy, as they may benefit from both diagnosis and therapy (e.g., ligation for variceal bleeding).

Lower Gastrointestinal Bleeding—Diagnostic Evaluation

Hematochezia is the passage of red blood from the anus Blood from the distal colon, rectum, or anus is fresh and usually bright red, whereas blood from the proximal colon is likely to be darker. Bleeding from the cecum or ascending colon may appear black but is not as shiny or tar-like as melena. Early colonoscopy for the detection of lower lesions may be the first diagnostic step (41). However, when the bleeding is significant it is often difficult to identify the source. A technetium-99-labeled red cell scan may identify the general location of bleeding; however, results are variable. If the source remains unknown, the next step is typically angiography. It can detect the bleeding site as well as allow treatment with intraarterial infusion of vasopressin or embolization (42).

Treatment/Management

General

It is important to understand the status of the primary disease, the expected survival, and the potential for cure in patients with GI hemorrhage. The long-term survival rate is poor and patients should not be subjected to unnecessary tests and procedures in their final days. The goal is to determine the source of the hemorrhage, stop the bleeding, and prevent recurrence. Start with a quick assessment of the hemodynamic status including vital signs and postural blood pressure. A sudden increase in pulse or postural hypotension may be the first indication of bleeding. The hematocrit should be followed; however, it may take hours to equilibrate. Packed red blood cells should be transfused until the hematocrit is greater than 25%. A coagulopathy should initially be corrected with four units of fresh frozen plasma; thrombocytopenia below 50,000/mm^3 requires platelet transfusions.

Upper Gastrointestinal Bleeding Treatment

To prevent stress ulceration and recurrent bleeding several medications are now available, although there is no evidence they are of benefit in the immediate posttreatment period (Table 18-5) (43). Endotracheal intubation to prevent aspiration may be necessary with massive upper GI bleeding. Supportive measures with antacids, H_2-receptor blockers, and blood products control the bleeding in 60% of patients with gastritis or ulceration. Endoscopic control using heater probe, bicap, YAG laser, and other modalities may provide temporary control of bleeding ulceration or tumors. If medical management fails, surgery should be considered. The decision to operate should also be based on the patient's potential quality of life and disease prognosis, as surgery is associated with high morbidity and mortality (44).

Drug	Dose
Antacid	2 tablespoons high-potency liquid, after meals and with heartburn
H_2 blocker	Ranitidine hydrochloride 150 mg p.o. twice daily
	Famotidine, 40 mg, at bedtime
	Nizatidine, 150 mg, at bedtime (duodenal)/ 150 mg p.o. b.i.d. (gastric ulcer)
Proton pump inhibitor	Omeprazole, 20 mg p.o. daily
Sucralfate	1 g twice daily
Prokinetic	Metoclopramide, 5–15 mg p.o. 4 times daily

TABLE 18-5. DRUGS USED TO PREVENT RECURRENT UPPER GASTROINTESTINAL BLEEDING

Variceal bleeding may be treated with endoscopic sclerotherapy or variceal ligation. Medical management is less effective, but octreotide acetate, a long-acting synthetic analogue of somatostatin (50 to 100-µg i.v. bolus followed by an infusion at 25–50 µg/hour) may reduce portal hypertension in acute variceal hemorrhage.

Balloon tamponade may temporize bleeding until more definitive therapy is begun. However, it is associated with a high rate of complications and mortality. Splenorenal and portosystemic shunts control variceal bleeding in a very select group of patients (45).

Lower Gastrointestinal Bleeding—Treatment

For lower GI bleeding, colonoscopy, radionuclide imaging, or mesenteric angiography may be required to identify the source. However, it may be difficult to determine the source due to significant bleeding when performing colonoscopy. If the bleeding rate is greater than 1 ml/ minute, selective mesenteric arteriography is the best procedure to localize the source. When it is not possible to localize the source, subtotal colectomy should be performed. In poor-risk patients, therapy with selective infusion of vasopressin or embolization of the bleeding vessel can be performed, but there is a risk of bowel infarction (46).

The Dying Patient

GI hemorrhage may be a terminal event in advanced cancer, and the family and professional team should be prepared as this can be a very distressing time. Bleeding may occur very rapidly, and the patient will die immediately of asphyxiation (upper GI bleed) or a precipitous drop in blood pressure resulting in cardiac arrest due to massive lower GI bleed. GI hemorrhage prevented a peaceful death in 2% of patients in a study of 200 hospice patients (47). The key to successful symptom management in the final days, particularly in the home, is preparation. It is important to have a plan to control these symptoms. Neuroleptics are the drugs of choice to sedate patients who have catastrophic bleeds (e.g., chlorpromazine, 25 mg i.v. slow push or 50 mg p.r. can be used). Benzodiazepines may increase anxiety (48), and unless the patient is having pain, opioids should not be used, as they may cause restlessness, diaphoresis, and hallucinations (49). It is helpful to have dark sheets and towels available to camouflage the bleeding. Although symptoms can be managed well in most, poor preparation precludes a comfortable death.

BILIARY OBSTRUCTION

Definition/Incidence

Biliary obstruction is the blockage of the flow of bile resulting in increased pressure in the biliary system. Malignant obstruction can occur anywhere in the biliary tree, but it most often affects the extrahepatic biliary tree or liver hilum. The incidence in malignant disease varies depending on the etiology and stage of disease. Extrahepatic biliary obstruction is common in carcinoma of the head of the pancreas. Less common tumors are in the ampulla, bile duct, gall bladder, or liver. Cholangiocarcinoma, metastatic tumor, or enlarged lymphatic nodes are other causes of biliary obstruction (50).

Pathophysiology/Etiology

Normally, the hepatocyte secretes bile. Blocking the flow raises pressure in the biliary system rendering the hepatocyte unable to secrete more. The pressure needed to stop secretion is 300 mm of H_2O, but there is evidence of cholestasis with lesser pressure. A neural or hormonal mechanism may be responsible for cholestasis before the necessary biliary pressure is reached.

Treatment/Management

Patients usually present in the advanced stage of the disease and surgical resection is rarely possible. Patients with symptomatic biliary obstruction should be evaluated for some type of biliary bypass procedure (51). Although survival is often limited, the symptoms, particularly pruritus, are quite distressing and less amenable to other treatments. Open surgical procedures have not been shown to prolong survival and are associated with greater morbidity and mortality than endoscopically placed stents (52). Unless the patient is moribund, a stenting procedure should be considered, as it may offer dramatic relief.

Stent placement with biliary drainage results in decreased serum bilirubin, and symptoms of pruritus usually resolve within 24–48 hours. The duration of palliation afforded by stenting depends on the underlying disease and the type of stent used to relieve the obstruction (53).

There are two types of endoscopically placed stents: selfexpanding metallic stents (SEMS) and plastic stents. The major drawback of plastic stents is occlusion with bacterial biofilm. This results in occlusion and recurrence of jaundice and requires one or more stent changes in 30–60% of patients. In randomized trials comparing plastic stents to SEMS in malignant bile duct occlusion, SEMS provided longer patency rates but had no survival advantage. In a three-arm study comparing plastic stent left in place until dysfunction occurred versus plastic stent routinely changed every 3 months versus SEMS, an initial success rate of 97% was obtained. The plastic stent not routinely changed had the poorest complication-free survival rate. The SEMS were the most cost-effective when life expectancy was greater than 6 months (54,55,56 and 57).

The method to control symptoms associated with biliary obstruction depends on the performance status of the patient, tumor type, and local professional expertise. It is important to remember that patients may appear gravely ill due to infection and obstruction, yet may improve dramatically with antibiotics and a procedure to relieve the obstruction.

HEPATIC FAILURE

Definition/Incidence

Hepatic failure is the severe inability of the liver to function normally, as evidenced by jaundice and abnormal plasma levels of ammonia, bilirubin, alkaline phosphatase, glutamic oxaloacetic transaminase, lactic dehydrogenase, and reversal of the albumin/globulin ratio. It quickly leads to failure of other organs. The hallmark of acute hepatic failure is hepatic encephalopathy and coagulopathy (58).

Pathophysiology/Etiology

Most hepatic failure, regardless of cause, results from massive coagulative necrosis of hepatocytes. Viral hepatitis accounts for approximately 70%, and drug ingestion (primarily acetaminophen) accounts for the majority of the remaining 30%. Malignant causes are associated with metastatic gastric carcinoma, carcinoid, breast cancer, small cell lung cancer, melanoma, leukemia, and lymphoma. Hepatic failure may be the presenting sign of malignancy in some cases (59). Sinusoidal obstruction with subsequent ischemia has been reported in metastatic liver disease. Occlusion of hepatic venous outflow may occur in the setting of intensive chemotherapy or bone marrow transplantation or recrudescence of hepatitis B virus after treatment.

Clinical Manifestations

Regardless of the cause, hepatic failure begins with nausea and malaise. It proceeds to accumulation of ammonia as a result of diminished urea formation, hepatic encephalopathy, cerebral edema, prolonged prothrombin time, rapidly rising bilirubin, metabolic changes, GI bleeding, sepsis, respiratory failure, renal failure, and cardiovascular collapse (60).

Hepatic Encephalopathy

Hepatic encephalopathy is a complex neuropsychiatric syndrome characterized by cognitive changes, fluctuating neurological signs, and electroencephalographic changes. In severe cases, irreversible coma and death occur (61,62). It results from severe hepatocellular dysfunction or intrahepatic and extrahepatic shunting of portal venous blood into the systemic circulation bypassing the liver. Toxic substances are not detoxified by the liver; this leads to metabolic abnormalities in the CNS. Most patients have elevated blood ammonia levels (63). Cognitive changes are due to excessive concentrations of gamma-aminobutyric acid. The role of endogenous benzodiazepine agonists is unclear but may contribute to hepatic encephalopathy (64). A partial response has been observed in some after administration of a benzodiazepine antagonist (flumazenil) (65). The most common predisposing factor is GI bleeding, which leads to an increase in ammonia production. Hypokalemic alkalosis, hypoxia, CNS-depressing drugs (e.g., barbiturates, benzodiazepines), and acute infection may also trigger hepatic encephalopathy (66,67).

Reversal of the sleep/wake cycle is among the earliest signs of encephalopathy. Mood disturbances, confusion, alterations in personality, deterioration in self-care and handwriting, and daytime somnolence also are seen. The diagnosis of hepatic encephalopathy is usually one of exclusion (68). There are no diagnostic liver function test abnormalities, although an elevated serum ammonia level is highly suggestive of the diagnosis (69). It is sometimes difficult to distinguish hepatic encephalopathy from other forms of delirium.

Portal Hypertension

Tumor burden may compress the hepatic blood vessels; this can result in portal hypertension, which causes collateral vessels in the esophagus and the stomach to become enlarged and tortuous (varices). Bleeding of the varices is likely because the liver is unable to synthesize vitamin K and clotting factors. Procedures to reduce the pressure include (a) a portal-systemic shunt, and (b) b-adrenergic blockade (e.g., propranolol hydrochloride), if not contraindicated (70).

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis occurs with ascites without an obvious primary source of infection. The ascitic fluid has low concentrations of opsonic proteins, which normally provide protection against bacteria. Paracentesis reveals cloudy fluid with a white cell count >500 cells/µl (>250 polymorphonuclear leukocytes). Common isolates are E. *coli* and pneumococci and, to a lesser extent, anaerobes. Empirical therapy with i.v. cefotaxime sodium (2 g every 8 hours for at least 5 days) and an aminoglycoside should be initiated if clinically appropriate (69).

Hepatorenal Syndrome

Hepatorenal syndrome is a disorder characterized by worsening azotemia, oliguria, hyponatremia, low urinary sodium, and hypotension, with structurally intact kidneys. It is diagnosed only in the absence of identifiable causes of renal dysfunction. Treatment is usually ineffective. Some patients with hypotension and decreased plasma volume may respond to volume expansion, but care must be taken to rehydrate slowly to avoid variceal bleeding (71).

Treatment/Management

Whenever possible, the inciting agent should be treated or eliminated. There is little role for liver transplant in the cancer patient. For most, treatment of the underlying disease provides the best method to reverse the process of hepatic failure. It may be useful to review adverse prognostic indicators in hepatic encephalophy (Table 18-6) before embarking on the intensive, supportive therapy necessary in those who survive.

Indicator	Value
Age	<10 yr, >40 yr
Cause	Idiosyncratic drug reaction, halothane, non-A, non-B hepatitis
Jaundice	>7 d before onset of encephalopathy
Bilirubin	>300 µmol/l (18 mg/dl)
Prothrombin time	>100 sec
Factor V level	<20%
Clinical status	Respiratory failure
	Rapid reduction in liver size
	Coma

TABLE 18-6. ADVERSE PROGNOSTIC INDICATORS IN HEPATIC FAILURE

Stenting biliary obstructions may provide relief of jaundice and pruritus. Paracentesis helps control symptomatic ascites. Neuropsychiatric symptoms are distressing and should be controlled with appropriate medications. Flumazenil, a short-acting benzodiazepine antagonist, may have a role in management of hepatic encephalopathy (65). Reducing oral protein intake in advanced cancer is rarely necessary. Administering lactulose, a nonabsorbable laxative sugar, may help. The initial dose is 30–50 ml every hour until diarrhea occurs; thereafter the dose is adjusted (15–30 ml three times daily) so that the patient has two to four soft stools daily (69).

In the terminal state, it may be appropriate to allow a deteriorating level of consciousness to progress and to forgo treatment. The neuropsychiatric symptoms are controlled with neuroleptics (if hallucinating, chlorpromazine 50–200 mg every 2–3 hours) or with diazepam (if agitated). The goal is to relieve distress without concern for the adverse effect of major tranquilizers on the mental status.

TENESMUS

Definition/Incidence

Tenesmus is a painful spasm of the anal sphincter with an urgent sensation of the need to defecate and involuntary straining, but little, if any, bowel movement. Patients complain of an abnormally frequent desire to defecate and a sensation that evacuation is incomplete. Rectal pain is not commonly caused by organic lesions, which more frequently result in tenesmus. It is a distressing, difficult to control problem. In the cancer patient it occurs most commonly in cancer of the rectum or after pelvic radiation.

Pathophysiology/Etiology

Tenesmus is thought to be a motility disorder of the rectum, with decreased compliance and high-amplitude pressure waves in the rectal wall. This results in an increased sensitivity to distention of the rectum. Rectal causes of tenesmus include impacted feces, carcinoma, rectal prolapse, rectal polyps, adenoma, hemorrhoids, fissure, proctitis, foreign body, abscess, and hemorrhoids. Infectious causes include *Shigell*a, *Campylobacte*r, and *Clostridium difficil*e.

In the patient with rectal cancer, tenesmus is usually an ominous sign, indicating circumferential growth or ulceration involving the sphincter muscle. Tenesmus typically occurs in the morning on arising and subsides as the day progresses. Accompanying perineal or buttock pain suggests involvement of the sacral nerve plexus. Patients presenting with this symptom complex are unlikely to be candidates for sphincter-saving procedures. Tenesmus can also be caused by damage from radiation therapy (acute and late effect) for rectal cancer or other pelvic structures (e.g., cervix, prostate, bladder, testes).

Treatment/Management

Treatment is based on the cause and is variably effective. Infectious causes should be treated with appropriate antibiotics. Radiation-induced tenesmus is a difficult problem. Symptoms usually resolve spontaneously within 2–6 months (72). Tenesmus and rectal bleeding have been treated with oral sulfasalazine combined with steroid enemas or sucralfate enemas (2 g in 20 ml of tap water) (73).

Among patients with rectal cancer, curative intent pelvic exenteration effectively controlled pain and tenesmus in 89% and palliative intent in 67% (74). However, this is a procedure associated with significant morbidity and should not be performed for the sole purpose of controlling pain. Radiotherapy may also provide symptomatic relief, but again, the primary purpose is to control the disease; it may be most useful in those who have not received chemotherapy (75). Metal expandable stents have been used successfully and are associated with little morbidity but may migrate (76). Lumbar sympathectomy produced complete relief of tenesmus in 10 of 12 patients with cancers in the pelvic region. Duration of relief was 3 days to 7 months (mean, 53 days). In this small series, the only complication was transient hypotension responding to intravenous fluids (77); however, mild, reversible bruising and stiffness at the needle insertion site often occur. Up to 20% of patients have limb pain, which develops after a 10- to 14-day latent period and spontaneously resolves after a few weeks. Major neurological deficits are uncommon when lumbar sympathectomy is performed by experienced pain practitioners, making lumbar sympathectomy one of the most important treatment modality currently available.

A general treatment plan should include a laxative and stool softener unless diarrhea is the prominent symptom, in which case an obstructing lesion should be ruled out. Care should be taken when prescribing roughage in those with previous radiation, as the bowel/rectal wall can be traumatized. Dexamethasone (4–16 mg daily) may provide some relief through its anti-inflammatory actions. The calcium channel antagonist nifedipine (10–20 mg two to three times daily) may help to relieve spasms. Epidural opioids and local anesthetics may also be helpful. Systemic opioids should be tried but are less effective, as in other forms of neuropathic pain. Traditional neuropathic pain treatment such as tricyclic antidepressants (e.g., amitriptyline hydrochloride) should be used with caution, as one of the main side effects is

constipation.

CONCLUSIONS

Because GI symptoms are so common in the general, healthy population it may be more difficult to evaluate them in those with cancer. Common symptoms may be disease-related or comorbidity unrelated to the cancer. Both may represent potentially life-threatening problems, and yet the decision to treat may not be clear if based on management guidelines for the general population. Decisions regarding treatment must be evaluated with an understanding of the goals of therapy, potential quality of life, and life expectancy. Consultation with GI specialists and ongoing communication with the patient and family help to provide the framework in which to make these often difficult decisions.

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19

ORAL MANIFESTATIONS AND COMPLICATIONS OF CANCER THERAPY

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GENERAL STRATEGIES

In 2002, a projected 1.2 million people in the United States will have been diagnosed with cancer (excluding skin cancers). Regardless of therapy (i.e., surgery, radiation therapy, and/or chemotherapy), recognition of the preexisting dental status is paramount for eliminating or decreasing the sequela of cancer treatment to the oral cavity. Many treatments have an effect on the normal and adjacent hard and soft oral tissues. As the cancer treatment becomes more intensified or complex in nature, the morbidity to the oral cavity must be taken into consideration.

Oral sequelae vary from patient to patient and have different stages and intensities, even with the same modality of treatment and stage of disease. Patient compliance and basic understanding of both short- and long-term effects of therapy is essential to alleviate potential problems. It is imperative for the patient's dentist to be familiar with the medical therapy and outcome expectations. Pretreatment dental assessment should be completed and addressed before cancer treatment to reduce morbidity.

Generally, surgical resections of any anatomical oral or pharyngeal structure compromises oral function. Many resections (i.e., soft palate, tongue, hard palate, mandible, or any combination of these) can be alleviated by means of intervention with maxillofacial prosthetics. Maxillofacial prosthetics restore function and cosmesis, with some limitations.

Chemotherapeutic toxicity can present with oral manifestations, which include mucosal ulcerations, local infection, and a wide range of oral discomfort.

Radiation therapy for head and neck cancers has a range of sequela in the oral cavity. This includes caries, mucositis, trismus, xerostomia, osteoradionecrosis (ORN), and secondary oral and fungal infections. All of these can be minimized—and many prevented—with pretreatment intervention.

Pretreatment strategies and intervention can decrease the risk of many oral complications. Regardless of treatment modality, comprehensive oral evaluation must include clinical and radiographical surveys to identify possible sources of dental infection and to eliminate ongoing caries, symptomatic periapical lesions, calculus, plaque, and clinical periodontal disease (including pericoronitis).

It is recommended that any patient anticipating intense chemotherapy or head and neck radiation therapy undergo dental screening at least 2 weeks before commencement of cancer therapy. This generally allows for proper healing of extraction sites (10–14 days), recovery of soft tissue manipulations, and restoration of teeth, all of which are critical in maintaining an overall integral mucosal continuity during treatment (1).

The dental assessment and subsequent treatment rendered should correlate to the overall prognosis of the tumor. Consultation with the referring physician is paramount to dental treatment strategies and decision-making.

One of the most important areas of concern in the mouth, which affects each cancer patient regardless of cancer treatment modality, is lack of or poor oral hygiene. It is advisable to perform a thorough root planing, scaling, and prophylaxis before commencement of any cancer treatment modality, with the exception of visible tumor if at the site of anticipated dental manipulation. These procedures reduce the incidence of oral complications by eliminating bacteria that could lead to local or systemic septicemia. The dentist must also be aware of the patient's total white blood cell count, absolute granulocyte count, and platelet count if the patient has received chemotherapy or is anticipating intense chemotherapy or bone marrow or stem cell transplant, especially if the patient requires dental extractions, oral biopsies, or periodontal surgery.

It is also important for the dentist, in the pretreatment stage, to establish baseline data to which subsequent examinations and treatment can be compared. These pretreatment strategies include eliminating or reducing periodontal disease, dental caries, defective restorations, ill-fitting prostheses, and third molar pathology; improving oral hygiene; and maintaining an intact and normal condition of all mucous membranes.

Patient and family education, counseling, and motivation are critical to the success of preventive strategies. The dentist has a monumental role and can contribute to an improved quality of life of the patient, especially if initiated in a pretreatment time frame. Minimization and oral manifestations of cancer treatment is a major concern for both dentists and physicians.

DIRECT STOMATOTOXICITY

Normally, cells of the mouth undergo rapid renewal over a 7-to 14-day cycle. Both chemotherapy and radiotherapy interfere with cellular mitosis and reduce the regenerative ability of the oral mucosa. Cancer chemotherapeutic drugs that produce direct stomatotoxicity include the alkylating agents, antimetabolites, natural products, and other synthetic agents (e.g., hydroxyurea and procarbazine hydrochloride) (2). Typical sequelae of these cytotoxic agents include epithelial hyperplasia, collagen and glandular degeneration, and epithelial dysplasia (3). Mucositis is an inevitable side effect of irradiation. The severity of the mucositis depends on the type of ionizing radiation, the volume of irradiated tissue, the dose per day, and the cumulative dose. As the mucositis becomes more severe, pseudomembranes and ulcerations develop. Poor nutritional status further interferes with mucosal regeneration by decreasing cellular migration and renewal (4).

Direct stomatotoxicity usually is seen 5–7 days after the administration of chemotherapy or radiotherapy. In the nonmyelosuppressed patient, oral lesions heal within 2–3 weeks (5). The nonkeratinized mucosa is most affected. The most common sites include the labial, buccal, and soft palate mucosa, as well as the floor of the mouth and the ventral surface of the tongue. Clinically, mucositis presents with multiple complex symptoms: The condition begins with asymptomatic redness and erythema and progresses through solitary, white, elevated desquamative patches (which are slightly painful to contact pressure) to large, contiguous, pseudomembranous, acutely painful lesions with associated dysphagia and decreased oral intake. Histopathologically, edema of the rete pegs is noted, along with vascular changes that demonstrate a thickening of the tunica intima and concomitant reduction in the size of the lumen and destruction of the elastic and muscle fibers of the vessel walls. The loss of basement membrane epithelial cells exposes the underlying connective tissue stroma with its associated innervation, which, as the mucosal lesions enlarge, contributes to increasing pain levels. Oral infections, which may be due to bacteria, viruses, or fungal organisms, can further exacerbate the mucositis and may lead to systemic infections. If the patient develops both severe mucositis and thrombocytopenia, oral bleeding may occur and may be very difficult to treat.

PATHOPHYSIOLOGY OF MUCOSITIS

Sonis et al. (6) proposed a hypothesis as to the mechanisms of the development and healing of mucositis. The hypothesis is based on both animal and clinical data, although it remains speculative to some degree. It describes mucositis as a complex biological process that occurs in four phases: (a) the inflammatory or vascular phase, (b) the epithelial phase, (c) the ulcerative or bacteriologic phase, and (d) the healing phase (Table 19-1). Each phase is interdependent and is a consequence of the effect of the chemotherapy or radiotherapy on the epithelium (as well as actions mediated by cytokines), the status of the patient's bone marrow, and the oral bacterial flora (6).

Phase 1: Inflammatory or vascular phase, d 0
Phase 2: Epithelial phase, d 4–5
Phase 3: Ulcerative or bacteriologic phase, d 6–12
Phase 4: Healing phase, d 12–16

Adapted from Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol* 1998;34(1):39, with permission.

TABLE 19-1. FOUR PHASES IN THE DEVELOPMENT OF MUCOSITIS

Phase I: Inflammatory or Vascular Phase

Cytokines such as tumor necrosis factor-a, interleukin (IL-1), and perhaps IL-6 are released from the epithelial tissue and adjacent connective tissue shortly after the administration of chemotherapy or radiotherapy. Most likely, the initiating event in the development of mucositis is local tissue damage caused by the cytokines. Additional concentrations of cytotoxic drugs in the mucosa may result from the increased vascularity caused by IL-1. Increased submucosal vascularity also occurs during this phase.

Phase 2: Epithelial Phase

Reduced epithelial renewal, with atrophy and ulceration, occurs as a result of both radiotherapy and chemotherapy, particularly with drugs affecting the S-phase of the cell cycle, whereby the impact is on dividing cells of the oral basal epithelium. The atrophy and ulceration that occurs is most likely exacerbated by locally produced cytokines as well as functional trauma. The first two phases usually occur from days 0–5 of therapy.

Phase 3: Ulcerative or Bacteriologic Phase

The most complex and symptomatic phase is phase 3, during which localized areas of erosion often become covered with a fibrinous pseudomembrane. This phase usually coincides with the patient's period of maximum neutropenia. Secondary bacterial colonization involving some gram-negative organisms occurs, and the gram-negative organisms provide a source of endotoxin, which stimulates further cytokine release from the connective tissue around the cells. The patient's condition is exacerbated by the cytokines as well as the nitric oxide that is released. This phase usually occurs from days 6–12 of therapy.

Phase 4: Healing Phase

The final phase usually consists of renewal in epithelial proliferation and differentiation, with normalization of the patient's peripheral white blood cell count and reestablishment of the local microbial flora. The healing phase usually takes place from days 12–16.

RISK FACTORS

Both direct and indirect factors appear to contribute to oropharyngeal mucositis. Direct factors include the chemotherapeutic agent, dosage, and schedule (Table 19-2); the total dose and days of radiotherapy; mucosal damage from such problems as ill-fitting dental prostheses, periodontal disease, microbial flora, and salivary gland dysfunction; and patient susceptibility. Indirect factors include myelosuppression, immunosuppression, reduced secretory IgA, and bacterial, viral, or fungal infections.

Anthracyclines
Daunorubicin
Doxorubicin
Epirubicin hydrochloride
Alkylating agents
Cyclophosphamide
Busulfan
Procarbazine hydrochloride
Thiotepa
Mechlorethamine hydrochloride
Taxanes
Docetaxel
Paclitaxel
Vinca alkaloids
Vinblastine sulfate
Vincristine sulfate
Vinorelbine tartrate
Antimetabolites
Methotrexate
5-Fluorouracil
Hydroxyurea
Cytosine arabinoside
Mercaptopurine
Thioguanine
Antitumor antibiotics
Actinomycin D
Bleomycin sulfate
Mithramycin
Mitomycin
Amsacrine

Adapted from Wilkes JD. Prevention and treatment of oral mucositis following cancer chemotherapy. *Semin Oncol* 1998;25:535, with permission.

TABLE 19-2. CHEMOTHERAPEUTIC AGENTS COMMONLY PRODUCING MUCOSITIS

A variety of patient-related factors have potential for affecting the development of mucositis after chemotherapy. It has been suggested that the repair of ill-fitting prostheses, extraction of offending teeth, elimination of periodontal disease, and effective oral hygiene can reduce the incidence and severity of mucositis. A patient might develop more severe mucositis if his or her nutrition is poor, through impairment of mucosal regeneration. Xerostomia that develops as a result of irradiation or drug use contributes significantly to the development of oral mucositis. Drugs that can result in xerostomia include antidepressants, opiates, antihypertensives, antihistamines, diuretics, and sedatives. Although both alcohol and tobacco can impair salivary function, it has been suggested that tobacco is associated with a decreased incidence of chemotherapy-induced stomatitis (7). One recent study involving 332 outpatients receiving chemotherapy revealed no significant differences in the incidence of mucositis between patients who wore dental appliances, had a history of oral lesions and a history of smoking, and practiced different oral hygiene regimens, and those patients who did not (8). These findings suggest that the risk factors for the development of chemotherapyinduced mucositis are many and complicated, and that further research is needed.

Reports on the effects of age on chemotherapy-induced mucositis development are conflicting. In general, younger patients are at increased risk for developing mucositis (7). Recent reports look at gender differences and the risk of mucositis. A meta-analysis of six North Central Cancer Treatment Group (NCCTG) trials involving 731 patients (402 men and 329 women) revealed that women reported stomatitis more often, and of greater severity, than men (9). In a pilot project using capsaicin for treating mucositis, data analysis revealed that women had a higher level of pain secondary to oral mucositis. It is also known that women are “supertasters” when tested with chemical relative phenylthiocarbamide/6-n-propyl-thiouracil; possibly, individuals who are supertasters and who therefore have more taste buds experience increased stomatitis (Table 19-3) (10,11).

Direct factors
Age
Gender
Preexisting dental hygiene
Nutritional status
Oral care during treatment
Radiation: dose, schedule
Chemotherapy: drug, dose, schedule
Xerostomia
Indirect factors
Myelosuppression
Immunosuppression
Reduced secretory IgA
Infections: bacterial, viral, fungal

TABLE 19-3. RISK FACTORS CONTRIBUTING TO MUCOSITIS

ASSESSMENT OF THE ORAL MUCOSA

A mucositis grading system allows the physician to assess mucositis severity in terms of both pain and the patient's ability to maintain adequate nutrition, so that a treatment plan can be appropriately constructed. Many different grading systems exist, most of which are based on two or more clinical parameters, including erythema, pain, and problems with eating (Table 19-4). An example of a common grading system is that proposed by the National Cancer Institute, which uses a numbering scale from 0 to 4. Grade 0 indicates no mucositis; grade 1, the presence of painless ulcers, erythema, or mild soreness; grade 2, the presence of painful erythema, edema, or ulcers that do not interfere with the patient's ability to eat; and grade 4, symptoms so severe that the patient requires parenteral or enteral support (12).

Grade	Criteria
0	Mouth pink No bleeding Mucosa moist No edema or infection No limitation to eating or drinking
1	Slightly increased redness of mouth 1–4 oral lesions Thinning of mucosa No bleeding or infection Mucosa moist Mild discomfort, burning sensation Possible avoidance of hot, harsh, or spicy foods
2	Moderate increase in mouth redness More than 4 discrete oral lesions, not coalescing Mucosa bleeds with manipulation Mucosa slightly drier Saliva slightly thicker Moderate edema White or yellow patches, infection present Eating of only bland, soft foods Avoidance of hot, spicy, or acidic liquids Moderate continual pain, necessitating intermittent, usually topical analgesics
3	Severe redness throughout oral cavity Multiple confluent ulcers Possible tonal denudation of oral cavity Marked xerostomia Severe edema White, yellow, or purulent patches Inability to eat or drink Inability to swallow saliva Severe, constant pain, necessitating systemic analgesia

Adapted from Western Cooperative for Cancer Nursing Research. Development of a staging system for chemotherapy-induced stomatitis. Cancer Nurs 1981;4:103, with permission.

TABLE 19-4. MUCOSITIS GRADING

Recently, new scoring systems have been developed for the assessment of oral mucositis. Sonis et al. (13) reported on a scale that uses an objective measure of mucositis, evaluating ulceration and pseudomembrane formation and erythema. Subjective outcomes of mouth pain, ability to swallow, and function were measured. Analgesia use for mouth sensitivity was also recorded. In the study that was conducted in nine centers, there was high interobserver correlation, with objective mucositis scores demonstrating strong correlation with symptoms.

At the 1989 National Institutes of Health consensus conference on oral complications of cancer therapy, clinicians and researchers agreed that effective prevention of mucositis requires a comprehensive patient examination to identify potentially complicating oral disease before the cancer therapy begins (14). Significant problems that must be corrected include poor oral hygiene, periapical pathology, third molar pathology, periodontal disease, dental caries, defective restorations, orthodontic appliances, ill-fitting prostheses, and other potential sources of infection. Bacterial and fungal surveillance cultures are not necessary, but prophylactic use of acyclovir should be considered in patients who are seropositive and at high risk for reactivating herpes simplex viral infection, such as those who undergo bone marrow transplant or who have prolonged and pronounced myelosuppression. If a diagnosis is made of a fungal, viral, or bacterial infection along with the mucosal lesions, prompt treatment is necessary to avoid the risk of systemic infection.

REMEDIES FOR THE PREVENTION AND TREATMENT OF MUCOSITIS

A standardized approach for the prevention and treatment of chemotherapy- and radiotherapy-induced mucositis is essential, although the efficacy and safety of most of the regimens have not been established. The prophylactic measures usually used for the prevention of mucositis include chlorhexidine gluconate (Peridex), saline rinses, sodium bicarbonate rinses, acyclovir, amphotericin B, and ice. Regimens commonly used for the treatment of mucositis and the associated pain include a local anesthetic such as lidocaine or dyclonine hydrochloride, magnesium-based antacids (Maalox, Mylanta), diphenhydramine hydrochloride (Benadryl), nystatin, or sucralfate. These agents are used either alone or in different combinations that compose a mouthwash. Other agents used less commonly include kaolin-pectin (Kaopectate), allopurinol, vitamin E, beta-carotene, chamomile (Kamillosan) liquid, aspirin, antiprostaglandins, prostaglandins, MGI 209 (marketed as Oratect Gel), silver nitrate, and antibiotics. Oral and sometimes parenteral narcotics are used to relieve the pain caused by mucositis. A new method that uses capsaicin for such pain relief is currently being studied.

Direct Cytoprotectants

Sucralfate

Sucralfate, an aluminum salt of sucrose orasulfate that has been used successfully to treat gastrointestinal ulceration, has been tested as a rinse for the prevention and treatment of mucositis. Sucralfate's mechanism of action appears to be the formation of an ionic bond to proteins in an ulcer site, thereby creating a protective barrier (15). Additionally, evidence points to an increase in the local production of prostaglandin E2 (PGE2), which results in an increase in mucosal blood flow, mucus production, mitotic activity, and surface migration of cells (16,17).

Anecdotal experience suggests that sucralfate might be useful in the prevention and treatment of chemotherapyinduced mucositis; however, data from the studies are conflicting. Solomon (18) reported a 55% objective response rate in patients receiving chemotherapy (19 patients), which was defined as a decrease in one grade on the Cancer and Leukemia Group B scale of oral toxicity. In 1984 and 1985, Ferraro and Mattern (19,20) reported encouraging results in the use of sucralfate for chemotherapy-induced mucositis. Two randomized, double-blind clinical trials also have evaluated sucralfate for the prevention of chemotherapy-induced mucositis. Pfeiffer et al. (21) found a significant reduction in edema, erythema, erosion, and ulceration in 23 of 40 evaluable patients receiving cisplatin and continuous infusion with 5-fluorouracil (5-FU) with or without bleomycin sulfate. Patients preferred sucralfate, although this preference failed to reach statistical significance. Ten of the patients did not complete the study, as the swishing of the sucralfate and the placebo aggravated chemotherapy-induced nausea. The authors suggested that, to help overcome this problem, the solution should have a neutral taste and should not be swallowed after swishing. In contrast, results from a similarly designed study, in which patients receiving remission-induction chemotherapy for acute nonlymphocytic leukemia were treated with sucralfate for mucositis, did not support the amelioration of mucositis (22). The latter study also concluded that chronic administration of the sucralfate suspension had no effect on the incidence of gastrointestinal bleeding and ulceration. The authors did note that some patients reported pain relief from sucralfate (22). A phase III study of sucralfate suspension versus placebo, recently completed by the NCCTG, revealed that in the 50 patients who developed stomatitis, the sucralfate suspensions provided no beneficial reduction in the duration or severity of 5-FU–induced mucositis (23). In addition, the sucralfate induced considerable additional gastrointestinal toxicity.

Sucralfate has also been tested in patients receiving radiotherapy. One study compared 21 patients who received standard oral care to the head and neck with 24 patients who received sucralfate suspension four times daily (24). Results revealed a significant difference in mucosal edema, pain, dysphagia, and weight loss in those patients receiving sucralfate. In a pilot study done by Pfeiffer et al. (25), sequential patients who received radiotherapy to the head and neck received sucralfate at the onset of mucositis. The majority of patients had a decrease in pain after sucralfate use. A doubleblind, placebo-controlled study with sucralfate in 33 patients who received irradiation to the head and neck reported no statistically significant differences in mucositis; however, the sucralfate group reported less oral pain and, in these

patients, other topical and systemic analgesics were started later in the course of radiation (26).

A prospective double-blind study compared the effectiveness of sucralfate suspension to that of diphenhydramine hydrochloride syrup plus kaolin-pectin on radiotherapyinduced mucositis. Data on perceived pain, helpfulness of mouth rinses, weekly mucositis grade, weight change, and interruption of therapy were collected daily. Analysis of the two groups revealed no statistically significant differences between them. A retrospective comparison of a group of 15 patients who had not used daily oral rinses with the preceding two groups suggested that the use of a daily oral rinse with a mouth-coating agent may result in less pain, may reduce weight loss, and may help to prevent interruption of radiotherapy because of severe mucositis (27).

Prostaglandins, Antiprostaglandins, and Nonsteroidal Agents

Prostaglandins are a family of naturally occurring eicosanoids, some of which have known cytoprotective activity. Dinoprostone, or PGE2, has been reported to be beneficial in healing both gastric ulcers and chronic leg ulcers (28,29). Pilot studies revealed the need for controlled clinical trials. In a pilot study undertaken by Kuhrer et al. (30), five patients received topical dinoprostone for chemotherapy-induced mucositis. Four of the five patients reported pain relief, with healing of the ulcers within 3–7 days. Kuhrer's group then tested the prophylactic efficacy of dinoprostone by applying it topically to one patient who was receiving chemotherapy and had developed previous episodes of mucositis, as well as to two other patients receiving total body irradiation (30). Only one of the patients who had received the dinoprostone and total body irradiation developed mucositis.

In a nonblinded study, ten patients who were receiving 5-FU and mitomycin with concomitant radiation for oral carcinomas were treated by Porteder et al. (31) with dinoprostone four times daily during treatment. The control group consisted of 14 patients who were receiving identical treatment. Eight of the ten patients who received dinoprostone were evaluable, and none developed severe mucositis, as compared with six episodes in the control arm.

A third pilot study conducted with 15 patients who received radiotherapy of the head and neck found that an inflammatory reaction in the vicinity of the tumor could be detected in only five patients treated with topically applied PGE2; none of the patients developed any bullous or desquamating inflammatory lesions (32). A double-blind, placebo-controlled study of PGE2 in 60 patients undergoing bone marrow transplant revealed no significant differences in the incidence, severity, or duration of mucositis. It. was noted that the incidence of herpes simplex virus was higher in those on the PGE2 arm; among those patients who developed herpes simplex virus, there was an increase in the severity of the mucositis (33).

Benzydamine is a nonsteroidal anti-inflammatory drug with analgesic, anesthetic, anti-inflammatory, and antimicrobial properties. Epstein and Stevenson-Moore (34) found, in a double-blind, placebo-controlled trial, that benzydamine produced statistically significant relief of pain from radiation-induced mucositis. Positive responses to benzydamine were reported in at least two other studies (35,36). The study conducted by Epstein and Stevenson-Moore (34) revealed not only a trend toward reduction in pain, but also a statistically significant reduction in the total area of ulceration, as well as the size of the ulcer. Another study demonstrated that when indomethacin, an antiprostaglandin, was given orally, it reduced the severity and delayed the onset of mucositis induced by radiotherapy (37).

Corticosteroids

No placebo-controlled studies of the use of corticosteroids for chemotherapy-induced mucositis have been reported, although two reports have focused on pilot work conducted with patients who received radiotherapy. Abdelaal et al.(38) reported the use of a betamethasone and water mouthwash in five patients receiving radiotherapy, whose mucosa remained virtually ulcer-free and who did not report any pain. The proposed mechanism of action of the steroid mouthwash was inhibition of leukotriene and prostaglandin production. Another pilot study compared 21 patients receiving radiotherapy, who used an oral rinse consisting of hydrocortisone in combination with nystatin, tetracycline, and diphenhydramine hydrochloride, with patients using a placebo rinse. Although only 12 of the 21 patients were evaluable by the end of the radiotherapy cycles, there was a statistically significant difference in mucositis and a trend toward a reduction in pain. No patients in the treatment group needed to interrupt the radiotherapeutic regimen, whereas three patients in the control group needed to interrupt their radiotherapeutic care (39).

Vitamins and Other Antioxidants

Vitamins in pharmacological doses have been used to treat mucositis. Vitamin E has been tested in chemotherapyinduced mucositis because it can stabilize cellular membranes and may improve herpetic gingivitis, possibly through antioxidant activity (40,41 and 42). The efficacy of vitamin E was demonstrated by Wadleigh et al. (43) in a randomized, double-blind, placebo-controlled study. Eighteen patients receiving chemotherapy were randomized to receive a topical application of vitamin E or a placebo. In the vitamin E-treated group, six of nine patients had complete resolution of their mucositis within 4 days of initiating therapy, whereas in the placebo group only one of nine had resolution of the lesions during the 5-day study period. This difference was statistically significant (43). Because both sucralfate and vitamin E provide some effectiveness in mucositis, a phase III study of sucralfate versus vitamin E for treatment-induced mucositis is currently under way.

Other antioxidants that have been used clinically include vitamin C and glutathione. Another antioxidant tested in a pilot study, azelastine hydrochloride, has been used in many allergic diseases and has been shown to be effective in the treatment of aphthous ulcers in Behçet's disease. Osaki et al. (44) reported on a study involving 63 patients who had head and neck tumors and received a combination of radiotherapy and concomitant chemotherapy. Twenty-six patients received regimen 1, which consisted of vitamins C and E and glutathione, whereas 37 patients received regimen 2, which consisted of everything in regimen 1 plus azelastine. At the completion of treatment, 21 of the patients in the azelastine arm remained at grade 1 or 2 mucositis, with six patients having grade 3 mucositis and ten having grade 4 mucositis. In the control group, grade 3 or 4 mucositis was induced in 6 and 15 patients, respectively, with only two patients having grade 1 mucositis and two having grade 2 mucositis. The azelastine was shown to suppress neutrophil respiratory burst both *in vivo* and *in vitro*, as well as suppressing cytokine release from lymphocytes. The authors concluded that a regimen including azelastine, which suppresses reactive oxygen production and stabilizes cell membranes, might be useful for the prophylaxis of mucositis due to chemoradiotherapy (44).

Beta-carotene, a vitamin A precursor with known effects on cellular differentiation, has been used for mucositis induced by radiation. Beta-carotene has been shown to produce regression of oral leukoplakia lesions (45). Mills (46) reported on the use of beta-carotene in treatment-induced mucositis. Ten patients receiving radiation interspersed with two cycles of chemotherapy were given beta-carotene 250 mg/day for the first 3 weeks of therapy, and then 75 mg/day for the last 5 weeks of therapy. The control group consisted of ten patients with oral cancer who were receiving identical treatment, but without the beta-carotene. At the end of treatment, there was a statistically significant difference in grade 3 to 4 mucositis in the beta-carotene group; there was no difference in grades 1 and 2 mucositis (46).

Silver Nitrate

Silver nitrate, a caustic agent, has been tested in radiationinduced mucositis. Because silver nitrate is known to stimulate cell division when it is applied to normal mucosa, it was thought that if it were applied before cytotoxic therapy, it might enhance repair and replacement of mucosa that was damaged by cytotoxic therapy. Maciejewski et al. (47) reported on 16 patients who received radiotherapy to bilateral opposing fields. Silver nitrate 2% was applied to the left side of the oral mucosa three times daily for 5 days before radiotherapy and during the first 2 days of radiotherapy. The right side of the oral mucosa was unpainted and served as the control. The study revealed significantly less severe mucositis and a decrease in duration of mucositis on the mucosa that was treated with silver nitrate (47). A second trial failed to confirm these results (48). Silver nitrate has not been formally evaluated in the treatment of chemotherapy-induced mucositis.

Miscellaneous Cytoprotectants

An uncontrolled study involving 98 patients with different malignancies who were receiving different medical regimens of either chemotherapy or radiotherapy reported that Kamil-losan liquid taken before and after the development of mucositis helped to prevent and decrease the duration of mucositis (49). In a placebo-controlled trial conducted by NCCTG, patients were randomized to receive chamomile or placebo, along with an established oral cryotherapy regimen. This study revealed that chamomile mouthwash did not reduce stomatitis associated with 5-FU chemotherapy (50).

Oshitani et al. (51) reported on the use of topical sodium alginate, an agent that has been shown to promote healing of esophageal and gastric mucosa, in radiation-induced mucositis. Thirty-nine patients with mucositis were randomized to receive either sodium alginate or placebo. Those who received sodium alginate had a reduction in both mucosal erosions and pain (51). Other topical agents used clinically for treatmentinduced mucositis include Kaopectate, diphenhydramine hydrochloride (Benadryl), saline, sodium bicarbonate, and gentian violet. Although these agents are used clinically for treatment-induced mucositis, no controlled clinical trials have yet established their efficacy.

Indirect Cytoprotectants

Hematological Growth Factors

Hematological growth factors currently are standard in the treatment of patients receiving high-dose chemotherapy. The effect of the hematological growth factors on decreasing the depth and duration of chemotherapy-induced neutropenia is well established. Lieschke et al. (52) examined the levels of neutrophil count and assessed

whether oral neutrophil count correlated with oral mucositis. In the study, the researchers found that the oral neutrophil count, similar to circulating systemic neutrophils, diminished to undetectable levels but recovered earlier than did the systemic circulating neutrophils. In those patients receiving granulocyte colony-stimulating factor (G-CSF), the mean cumulative mucositis score was less than that in patients who did not receive G-CSF (52).

Gabrilove et al. (53) reported on 27 patients receiving methotrexate, vinblastine sulfate, doxorubicin, and cisplatin for bladder carcinoma, along with escalating doses of G-CSF. The patients received the G-CSF on their first cycle of chemotherapy but did not receive it on their second cycle. Significantly less mucositis was seen during the cycle in which the patients received the G-CSF. In this study, a bias may have been inherent, as there is perhaps cumulative chemotherapeutic toxicity such that with each cycle of chemotherapy, the severity of mucositis increases.

Bronchud et al. (54) treated 17 patients with breast or ovarian carcinoma who were receiving escalating doses of doxorubicin with G-CSF support. In this study, the G-CSF did not prevent severe mucositis. In a fourth study using G-CSF, 41 patients receiving chemotherapy for non-Hodgkin's lymphoma received G-CSF, whereas 39 received chemotherapy without G-CSF. In those patients who did not receive G-CSF, the main cause of treatment delay was neutropenia, whereas in those patients who did receive G-CSF, the main cause of treatment delay was mucositis (55).

In a small prospective study, patients who received platinum, infused 5-FU, and leucovorin calcium plus granulocyte-macrophage colony-stimulating factor (GM-CSF) had a decreased incidence of grade 3 mucositis (56). In a study comparing patients undergoing bone marrow transplantation in whom GM-CSF was used to historical controls, recovery of neutrophils was more rapid in the GM-CSF group; however, there was no difference in the severity of mucositis, nor in duration of hospitalization (57). At this time, the use of CSFs in the prevention or treatment of mucositis is investigational.

The effect of other biologically active factors on mucositis development is currently being studied. *In vitro* studies have shown that epidermal growth factor (EGF) not only is present in saliva but also has the ability to affect growth, cell differentiation, and cell migration (58,59). It is known that EGF induces chemotaxis of oral epithelial cells, indicating that it may be important in maintaining the integrity of the oral epithelium, especially in wound healing. Patients with peptic ulcers have been shown to have significantly lower levels of EGF in their saliva, suggesting that EGF may be involved in either protection or repair (60). In an animal study in which the animals received either 5-FU with an infusion of EGF for 7 and 15 days or a placebo, the animals that received the EGF experienced increased mucosal breakdown. The results of the study indicate that chemotherapy-induced mucositis depends on the rate of epithelial cell growth. The timing of administration of the EGF in relation to the chemotherapy may determine whether the patient develops increased oral toxicity or repair of the mucosa (61). In a study conducted by Sonis et al. (62), hamsters received EGF versus placebo using four different treatment schedules. In this study, delayed exposure to EGF delayed the onset of mucositis, but it had no beneficial effects on the duration or severity of mucositis.

Tumor growth factor-b3 (TGF-b3) is an inhibitor of epithelial cell growth. In a study using Syrian hamsters done by Sonis et al. (63), the topical application of TGF-b3 resulted in a decrease in the severity and duration of chemotherapy-induced mucositis. In another study performed by Spijkervet and Sonis (64) with Syrian hamsters, the topical application of TGF-b3 significantly reduced the severity and duration of ulcerative mucositis induced by 5-FU. In animal experiments, IL-1 and IL-11 demonstrated a cytoprotective effect (65,66 and 67).

Antimicrobials

Many conflicting studies have been published on the use of chlorhexidine gluconate mouthwash for both alleviating mucositis and reducing oral colonization by gram-positive, gram-negative, and *Candida* species in patients receiving radiotherapy, chemotherapy, or bone marrow transplantation. In 1990, Ferretti et al. (68) demonstrated in a randomized, controlled trial that prophylactic chlorhexidine gluconate mouthwash reduces oral mucositis and microbial burden in cancer patients receiving chemotherapy. The majority of studies since that time have not demonstrated a reduction in mucositis in patients receiving intensive chemotherapy and using chlorhexidine gluconate mouthwash (69,70 and 71). However, Weisdorf et al. (70) and Epstein et al. (71) did demonstrate a reduction in oral colonization by Candida species and oral candidiasis. Ferretti et al. (72) found that the use of chlorhexidine gluconate rinse for the prevention of mucositis was not effective, although there was a reduction in streptococcal counts. Spijkervet et al. (73), in a placebo-controlled, double-blind study, revealed that the colonization index of viridans *streptococci* was reduced after 5 weeks of chlorhexidine gluconate treatment, although such therapy did not decrease the colonization of *Candida* species, *Streptococcus faecalis*, *staphylococci*, *Enterobacteriaceae*, *Pseudomonadineae*, and *Acinetobacter* species, and there was no difference in the development and severity of mucositis. A recent randomized, doubleblind study comparing chlorhexidine gluconate mouthwash to placebo in 25 patients receiving radiotherapy revealed that there was a trend toward more mucositis as well as mouthwash-induced discomfort, taste alteration, and teeth staining in the chlorhexidine gluconate arm (74). The overall statistical data led to the conclusion that chlorhexidine gluconate may result in improved oral hygiene, but the discomfort of using the rinse negates its minimal benefits.

The endotoxins of aerobic gram-negative bacilli are implicated in the etiology of mucositis. A study by Spij-kervet et al. (75) postulated that lozenges containing 2-mg polymyxin E, 1.8-mg tobramycin, and 10-mg amphotericin B (PTA) four times daily on the oropharyngeal flora would mediate and control mucositis. These researchers compared 15 irradiated patients using PTA and two other groups of 15 patients each, one of which was using 0.1% chlorhexidine gluconate and the other of which was using placebo. In the selectively decontaminated group, the severity and extent of mucositis was significantly reduced as compared with that in the chlorhexidine gluconate and placebo groups ($p<.05$). Clinically, all patients in the lozenge group showed erythema only, whereas 80% of both the placebo and chlorhexidine gluconate rinse patients experienced severe mucositis with extended pseudomembranes from the third week of irradiation. No nasogastric tube feedings were needed in the PTA group, as compared to 30% of patients in the other groups (75). The potential role of PTA lozenges remains to be clarified.

IB-367, a broad-spectrum antimicrobial peptide found in porcine leukocytes, was tested in a hamster model (76). The results indicated that mucositis scores were significantly lower in hamsters given topical IB-367, as compared to those receiving placebo. Although further study is needed, IB-367 might improve clinical outcomes in patients at risk for the development of mucositis (76). Another antimicrobial, nystatin suspension, has been studied in the prophylaxis of candidiasis in leukemia and bone marrow transplantation patients. The majority of publications do not support the use of nystatin (77,78,79,80,81,82,83 and 84).

Pharmacological Modulation

Another agent that has been evaluated for the prevention and treatment of oral mucositis induced by 5-FU chemotherapy is allopurinol. The rationale for allopurinol mouthwash was based on data that systemic allopurinol was able to decrease 5-FU–induced toxicity by inhibiting the enzyme orotidylate decarboxylase and formation of the metabolites of fluorodeoxyuridine monophosphate and fluorouridine (85).Two pilot studies support the use of allopurinol for oral mucositis. The study by Clark and Selvin (86) revealed that allopurinol mouthwash substantially decreased the incidence and severity of mucositis in six patients who received bolus 5-FU chemotherapy. Another pilot study, involving 16 patients receiving 5-day intravenous 5-FU infusions and using allopurinol mouthwashes four to six times daily, also found that the allopurinol alleviated the mucositis in all patients (87). After the success of these pilot studies, the use of allopurinol became routine medical practice in many institutions. The efficacy of allopurinol was tested by the NCCTG and the Mayo Clinic in a randomized, doubleblind clinical trial. Seventy-five patients were assigned to receive allopurinol mouthwash or placebo while they received their first 5-day course of 5-FU with or without leucovorin calcium. This study demonstrated no protective effect against 5-FU–induced mucositis by the allopurinol regimen (88).

Leucovorin calcium has been used in combination with methotrexate to help decrease the oral mucositis that occurs with methotrexate. In a pilot study involving 19 patients who received edatrexate for non-small cell lung carcinoma, less mucositis was seen than was anticipated (89). There is. decreased mucositis when reduced folates are given systemically after methotrexate administration (90). In a small crossover study, administration of leucovorin calciumhyaluronidase mouthwashes did not reduce the severity of mucositis induced by high-dose methotrexate (91).

Glutamine administration in animal studies has been shown to lead to a reduction in both morbidity and mortality of animals who have received a variety of chemotherapeutic agents, including methotrexate. The glutamine both preserved the morphological structure of the gastrointestinal tract and reduced the incidence of bacteremia (92,93). In a randomized trial of 28 patients with gastrointestinal cancers who received 5-FU and folinic acid, no effect on oral mucositis was seen in the group who also received 16 g glutamine daily for 8 days as compared to the group who received a placebo. The authors concluded that perhaps both the dose and duration of exposure to the glutamine were not sufficient to show a decrease in mucositis (94).

According to laboratory data, another agent that protects host tissues selectively from 5-FU's toxic effects without loss of antitumor effect is uridine (95). A study was conducted involving 29 patients with advanced malignancies who received N-phosphoracetyl-disodium l-aspartic acid and methotrexate, each at 250 mg/m^2 , followed 24 hours later by increasing doses of 5-FU (600 to 750 mg/m^2), with a leucovorin calcium rescue and uridine rescue for a 72-hour infusion. The uridine allowed dose escalation of 5-FU to 750 mg/m^2, with a decrease in all toxicities of the 5-FU except mucositis, which remained as the only significant chemotherapy-induced toxic effect (96). Perhaps additional studies with oral uridine will reveal a reduction of the toxicity from mucositis.

A pilot study using propantheline bromide, an anticholinergic agent that causes xerostomia, was performed to test whether the incidence of mucositis could be reduced when patients received etoposide (97). It was hypothesized that the mucosal toxicity might be related to salivary excretion of etoposide after its systemic administration. Propantheline bromide or placebo was given to 12 patients. The results revealed a decrease in the incidence and severity of mucositis in the patients who received the propantheline bromide (97).

Cryotherapy

Cryotherapy, in the form of ice chips and flavored ice pops, has been used to prevent mucositis. The NCCTG and the Mayo Clinic undertook a controlled, randomized trial of oral cryotherapy for preventing 5-FU–induced mucositis and found that cryotherapy is helpful in reducing the severity of 5-FU–induced mucositis (98,99). After this study had been completed, another was undertaken in which patients were randomized to receive 30 minutes versus 60 minutes of cryotherapy (100). A total of 178 evaluable patients were studied. Both cryotherapy groups had similar degrees of mucositis. The conclusion was to continue to recommend the use of 30 minutes of oral cryotherapy for patients receiving bolus-intensive courses of 5-FU–based chemotherapy (100). An additional study, conducted after the original study reported by the NCCTG and the Mayo Clinic, confirmed that oral cryotherapy can reduce 5-FU– induced mucositis (101).

Laser

Laser as a palliative methodology for mucositis has only recently begun to be investigated. The potential for lesion and pain control using laser was initially studied in an animal model. In a study of four groups of animals having a mucosal lesion, three groups received impulse laser exposure from 60 to 600 pulses, and one group remained untreated (102). The only group that demonstrated more rapid resolution of the mucosal lesion (14 versus 21–25 days) was the group that received the 600 pulsed exposures.

A preliminary report revealed that laser may be beneficial in reducing the severity and duration of mucositis. A study involving 20 patients with different cancers and chemotherapeutic protocols (who served as the controls) and 16 patients who received laser therapy (composing the treatment group) revealed reduced duration of the mucosal lesions, from a mean of 19.3 days in the control arm to 8.1 days, in the treatment arm (103). At this time, double-blind, randomized trials are needed to verify these earlier reports.

Anesthetic Cocktails

Several anesthetic cocktails, made up of agents such as viscous lidocaine (Xylocaine) or dyclonine hydrochloride, have been used with some success (104). The anesthetic agents do relieve the patient's pain; however, this relief is only temporary and also prevents taste perception, which can further interfere with food intake. Other analgesics and mucosal coating agents that can control pain include kaolin-pectin, diphenhydramine hydrochloride, and dental anesthetics such as Orabase and Oratect Gel. In a prospective, double-blind study involving 18 patients, viscous lidocaine with cocaine 1%, dyclonine hydrochloride 1%, kaolin-pectin solution, diphenhydramine hydrochloride, and saline solution were compared with a placebo. The dyclonine hydrochloride 1% provided the most pain relief, whereas dyclonine hydrochloride with viscous lidocaine and cocaine 1% provided the longest pain relief (105). Although clinicians use many of the topical agents, little experimental evidence exists to establish the efficacy of many of them (106).

Capsaicin

Capsaicin, the active ingredient in chili peppers, is a remedy that has been used for many different pain syndromes through the years and that may prove beneficial for mucositis pain induced by chemotherapy and radiotherapy. Several studies support the medical efficacy of locally applied capsaicin in a cream vehicle in neuropathic pain syndromes. A large, multicenter trial involving 277 patients demonstrated that topically applied capsaicin used for up to 8 weeks significantly reduced pain and improved quality of life in both postherpetic neuralgia and diabetic neuropathy (107,108 and 109). Other neuropathic pain syndromes for which capsaicin has been shown to be effective include postmastectomy pain (110), stump pain (111), trigeminal neuralgia (112), reflex sympathetic dystrophy (113), and Guillain-Barré syndrome (114). Topical capsaicin has also been shown to decrease the pain associated with rheumatoid and osteoarthritis (115), and intranasal capsaicin spray has been shown to reduce the pain associated with cluster headaches (116). Topical capsaicin has been shown to improve the rate of reepithelialization of wound healing in minipigs; thus, it may prove to be efficacious in wound healing in humans (117).

In a pilot project, capsaicin in a candy vehicle (cayenne pepper candy) was given to patients with therapy-induced mucositis. Patients were instructed to allow the candy to dissolve in the mouth without chewing it. After the candy had dissolved, the burn produced by the candy was allowed to fade. The patients rated their pain before and after eating the candy. The reduction in pain was highly statistically significant (10,11). A double-blind, placebo-controlled study is under way to test the efficacy of oral capsaicin for pain control.

Narcotics

Many of the agents previously mentioned may have some value in preventing mucositis or palliating the pain; however, very few controlled clinical trials have established their efficacy. At present, no standard treatment has been defined for the prevention or treatment of mucositis. When mucositis is severe and interferes with nutritional intake and quality of life, it is appropriate to use any of the treatments that have already been cited, as well as oral, transmucosal, or if necessary, parenteral narcotics. Currently, a study is under way to investigate the usefulness of transmucosal fentanyl (Actiq) in the treatment of mucositis (Table 19-5). A recent article also reported on the successful use of topical opioids (morphine sulfate 0.08% gel, prepared with taste supplements) in treating mucositis in a patient who was terminally ill (118). To discover an efficacious treatment, it is essential to continue studies of the treatments already available and to develop any promising new approaches.

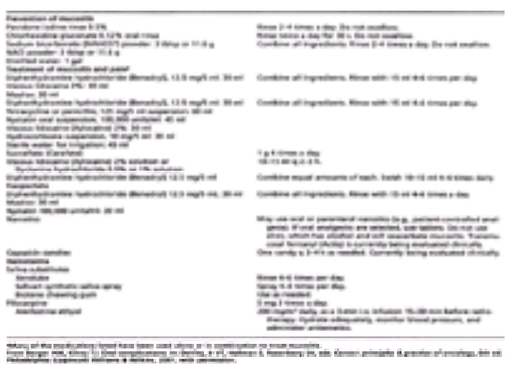

TABLE 19-5. FORMULARY OF COMMON REMEDIES FOR ORAL COMPLICATIONS

HEAD AND NECK RADIOTHERAPY—PRETHERAPY DENTAL EVALUATION AND INTERVENTION

Both short- and long-term effects of therapeutic radiation therapy to the head and neck regions involve the oral cavity. These changes can lead to mucositis, xerostomia, radiation caries, loss of taste, trismus, and possibly radionecrosis (119). The oral sequelae may cause substantial problems during and after radiation therapy. Acute incidents of focal infection (e.g., periodontal or periapical infection) and severe mucositis occasionally may necessitate an adjustment or an interruption of the radiation therapy schedule. Most preventive procedures described in the literature are based on clinical experience. The result is a great diversity in treatment policies and preventive approaches in daily dental practices. Most publications involving the head- and neck-irradiated patient are concerned with one sequelae. Usually each institution usually has its own protocol and treatment standards, which are extremely concise. The primary issues of patient care before radiation exposure include screening, consequential treatment, patient motivation, and initiation of preventive measures. Management of the patient during radiation therapy is characterized by prevention and treatment of acute complications and sequelae by radiation exposure of which are of short duration. Attention also must be addressed at the postradiation situation, as prevention and treatment of chronic dental disease must be addressed with close follow-up and continued care of the head- and neck-irradiated patient.

To maximize the effect of screening patients preradiation therapy, adequate time must be considered for dental treatment, fabrication of fluoride carriers, radiation-protective mouthguards, and wound healing (120). It is suggested that this initial appointment for dental and oral evaluation be made immediately after the diagnosis of oral cancer, within 2 weeks before the onset of radiation therapy and before simulation. At the initial appointment, the patient dentition should be examined and checked for carious lesions; defective restorations, which are sources of potential irritation of the oral mucosa, should be replaced, and the periodontium and the vitality of the pulp must be evaluated. Periodontal status is the major dental consideration and should be thoroughly screened by measuring pocket depth, as well as assessing furcation involvement. Oral hygiene must be evaluated and assessed. Plaque and gingival hemorrhage on dental pocket probing are very helpful in deciding the treatment plan regarding dental intervention (e.g., preradiation extractions). The patient's dental awareness is of utmost importance at this evaluation. The patient must possess motivation to maintain dentition properly and must comply completely with the prescribed oral hygiene preventive regimen. The oral mucosa and alveolar

process should be evaluated and considered for possible future prosthetic intervention. Areas evaluated for ulcerations, fibromas, irritation, hyperplasia, bony spicules, and tori should be included in this evaluation. The fit of dentures should be checked because ill-fitting dentures are a potential source of irritation after mucosal surfaces are exposed to radiation, with the possibility of ulceration to underlying bone (120a). The maximum mouth opening should be recorded before radiation therapy as a baseline to compare the interarch distance at different times post-radiation therapy to evaluate the degree of trismus. Trismus can be anticipated if the temporal mandibular joints and other muscles of mastication are included in the field of radiation. Decayed, missing, and filled rates of teeth should be recorded, as well as a generalized periodontal evaluation including gingival and plaque indices. A panoramic radiograph supplemented by intraoral radiographs, when necessary, is most suitable for detection of periodontal disease, periapical infections, cyst, third molar pathology, unerupted or partially erupted teeth, and residual root tips.

As a general rule, any teeth with acute and symptomatic periodontal problems should be extracted before head and neck radiation therapy. The decision of extractions of asymptomatic teeth prior to the commencement of radiation therapy can be based on several factors of importance. These include tumor prognosis and the patient's motivation to comply with the preventive regimen. A lack of motivation on the part of the patient should lead to a decision to extract questionable teeth before radiation therapy. Radiation exposure, type, portal field, fractionization, and total dosage are also part of the decision formula (120b), in addition to tumor prognosis and expediency of control of the cancer (Table 19-6).

Advanced carious lesions with questionable pupal status or pupal involvement
Extensive periodontal lesions
Moderate to advanced periodontal disease (pocket depth in excess of 5 mm, especially with advanced bone loss, mobility, or root furcation involvement)
Residual root tips not fully covered by alveolar bone or showing radiolucencies
Incompletely erupted teeth that are not fully covered by alveolar bone, or that are in contact with the oral involvement

From Berger AM, Kilroy TJ. Oral complications. In: DeVita, Jr VT, Hellman S, Rosenberg SA, eds. *Cancer: principles & practice of oncology.* 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2001, with permission.

TABLE 19-6. INDICATIONS FOR EXTRACTIONS (PRERADIATION THERAPY)

Deeply impacted teeth that are completely covered by bone and mucosa are usually left without risk of late problems. Teeth that are class II or III mobility and would not be beneficial as abutment teeth for retention of a prosthesis should also be considered for extraction preradiation therapy. Extractions of residual root tips, impacted teeth, and other focus which can be of potential infection should be performed atraumatically with regarded tissue handling. Alveolectomy and primary wound closure are considered for eliminating sharp ridges and bone spicules, which could project to the overlying soft tissues. This is particularly important for prosthetic consideration because negligible bone remodeling can be expected after radiation therapy. Generally, dental extraction can be performed in the general dental office.

Nonvital teeth located in the portal fields that are without periapical radiolucency and are not causing symptoms should be treated endodontically. In mandibular molars, endodontics with possible retrograde filings are preferred because of an increased ORN risk in this region. Teeth with small amount periapical granulomas, without periodontal involvement, and which are important for oral function or rehabilitation should be treated with apicoectomies.

Adequate time for healing of extraction sites before radiation therapy is essential. Healing times of 14–21 days generally are considered safe and should be the rule. Antibiotics are not routinely recommended because there is no evidence that they influence healing in the absence of infection. Careful examination of extraction sites must be performed before radiation therapy commences. Communication between the dentist, patient, and radiation therapist is the cornerstone for successful maintenance of the oral cavity. Patients are very susceptible to dental caries (decay) at the cervical areas of all teeth after radiation therapy to the head and neck region. Patients are instructed about effective daily plaque removal. Instructions regarding use of soft toothbrushes and a fluorinated toothpaste is essential. The patients are told to brush and floss at least three to four times a day, beginning immediately. A neutral 1% sodium fluoride gel, self-applied every night for 5 minutes (120c), a brush-on gel, or a fluoride mouth rinse is prescribed in conjunction with strict oral hygiene measures. Acidulated gels are usually not prescribed because they might lead to significant decalcification without sufficient remineralization potential in the presence of xerostomia. In addition, sodium fluoride preparations are preferred to stannous fluoride because the latter has unpleasant side effects (e.g., bad taste, sensitivity of teeth and gingiva, and staining arrested lesions). Daily compliancy of fluoride for the rest of the patient's life is more of an issue than the modality of fluoride application.

Radiation-induced dental effects primarily depend on salivary changes and occur when the glands are included in the field of treatment, rather than on direct irradiation of the teeth themselves. Direct irradiation of teeth may alter the organic or inorganic components in some manner, making them more susceptible to decalcification or hypocalcification. There have been no clinical studies to support the possibility that radiation therapy directly effects the pupal chamber; however, many teeth in the direct irradiated field could be desensitized thus, if early caries involve the nerve, might be asymptomatic. Thus it is essential for meticulous home care including daily fluoride application.

Oral candidiasis is a common acute and chronic oral sequela of head and neck radiation therapy. These lesions can be removable (whitish) chronic or hyperplastic (nonremovable), chronic erythematous (diffused as patchy erythema), and frequently appear as angular cheilitis (first signs or symptoms). Treatment of oral candidiases includes mycostatin (troches), nystatin (liquid or ointment), or clotrimazole. Pseudo membranous candidiasis is successfully treated topically. Chronic candidiases usually require much longer treatment and may require oral ketoconazole, fluconazole, or intravenous amphotericin B.

XEROSTOMIA

Xerostomia in head- and neck-irradiated patients is a major sequela. Its magnitude is dependent on the radiation dosage, location, and volume of exposed salivary glands. However, significant xerostomia has not been shown as a sequela in patients treated with chemotherapy alone. The degree of xerostomia is usually reported subjectively by both patients and clinicians, and can affect oral comfort, fit of prostheses, speech, and swallowing. Many of the enzymes (mucin) found in xerostomia patients contribute to the growth of caries-producing organisms. This sequela of a decrease in quantity and quality of saliva can be devastating to the dentition with the formation of caries. It has been previously mentioned that oral hygiene regimens, with the use of water/saline and daily fluoride application along with brushing teeth at least three times daily, can reduce colonization and proliferation of oral pathogens.

Sialogogues such as pilocarpine have recently been investigated and suggested to stimulate residual salivary parenchyma pilocarpine. Improvement has been reported in some patients (121,122 and 123). Extreme caution in the use of pilocarpine is important due to reported side effects of glaucoma, cardiac problems, and sweating.

A randomized, controlled trial of standard fractionated radiation with or without amifostine, administered at 200 mg/m^2 as a 3-minute i.v. infusion 15–30 minutes before each fraction of radiation, was conducted in 315 patients with head and neck cancer. Patients were required to have at least 75% of both parotid glands in the radiation field. The incidence of grade 2 or higher acute xerostomia (90 days from the start of radiotherapy) and late xerostomia (9–12 months after radiotherapy), as assessed by the Radiation Therapy Oncology Group Acute and Late Morbidity Score and Criteria, was significantly reduced in patients receiving amifostine. At 1 year after radiotherapy, whole saliva collection after irradiation showed that more patients given amifostine produced 0.1 g of saliva (72% versus 49%). In addition, the median saliva production at 1 year was higher in those patients who received amifostine (0.26 g versus 0.10 g). Stimulated saliva collections did not show a difference between treatment arms. These improvements in saliva production were supported by the patients' subjective responses to a questionnaire regarding oral dryness (124).

Artificial saliva, usually with carboxymethcellulose as a base, has not been demonstrated to increase oral cavity comfort. Sugarless gum and hard candies are frequently used by patients for comfort, with reported subjective improvement. The dental team should also encourage the patient to quit or reduce the use of tobacco and alcohol.

LONG-TERM EFFECTS OF RADIATION

The long-term effects of head and neck radiation therapy can include soft tissue fibrosis and obliterative endoarteritis. These changes become more substantial over time, including trismus and non- or slow-healing mucosal ulcerations. Surgical wounds (i.e., extraction sites) in the irradiated area usually heal slowly. The muscles of mastication or the temporal mandibular joint (if in the field of radiation therapy) can become fibrotic with clinical entities. Early exercises, with trismus appliances postradiation, can prevent this sequela. Use of tongue depressors taped together, along with 10-minute sets of exercise 10–15 times a day, can be effective in reducing trismus. Fibrosis of the muscles of mastication (temporalis, masseter, external and internal pterygoids), can occur even 1 year postradiation; thus, jawopening

exercises should be commenced after mucositis has subsided, and should be continued for over a year after completion of radiation therapy.

ORN is a relatively uncommon clinical entity and is now described as related to hypocellularity, hypovascularity, and ischemia of tissues rather than of a bacterial origin (125). This process can be spontaneous, but is usually initiated after trauma, such as dental extraction. This process can progress to pathological fracture, infection of surrounding soft tissues, and severe pain. Most studies have reported ORN after tooth extractions, postradiation or preradiation, in cases in which there hadn't been 10–14 days of healing before commencement of radiation therapy. The risk of ORN does not diminish over time, and some authors believe it can even increase many years post-radiation therapy.

Some authors maintain that traditional treatment of ORN with antibiotics and surgical débridement and curettage have been unsuccessful. Recent literature supports hyperbaric oxygen to boost tissue oxygenation in damaged irradiated wounds for anticipated difficult extractions, as well as for patients with radiographical interpretation of trabicular bony pattern avascularity and thin and telegentasia covering mucous membranes or gingiva (126). Further controlled and randomized clinical studies are needed to support hyperbaric oxygen as adjunctive treatment. Dental extractions after radiation therapy require consultation between dentist and radiation oncologist to minimize the risk of ORN. Most reported studies demonstrate a low incidence of ORN if preradiation dental consult and appropriate treatment (e.g., extractions) are rendered (127,128 and 129). Follow-up and recall of the head and neck patient for dental preventive maintenance and treatment are essential to prevent sequelae in the oral cavity.

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20

PRURITUS

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Like the sensation of pain, pruritus (itching) can diminish the quality of life in cancer patients. Because of the distress pruritus may cause, the cancer clinician should be aware of its importance and its management. Pruritus in cancer patients may be attributable to a primary skin disease, a coexisting medical condition, a medication, or the cancer itself. Indeed, to quote Krajnik and Zylicz, “There is no one cure for all pruritic symptoms. Better understanding of mechanisms of pruritus may help develop better treatments” (1). Beyond this, there have been articles, chapters, and texts by noted authorities (1,2,3,4,5,6,7,8,9,10,11,12 and 13). This chapter focuses on pruritus in cancer patients and reviews its etiology, diagnosis, and management. Readers should bear in mind that patients with cancer are eligible to be affected by the same pruritic conditions that noncancer patients may acquire, in addition to cancer- and cancer treatment-associated pruritic conditions.

PRURITIS SENSATIONS

In simplest terms, *pruritus* is the sensation that provokes scratching behavior. Like the sensation of pain, objective analysis cannot easily confirm the presence or severity of pruritus. Nevertheless, patients are generally thought to be reliable in their assessment of pruritus severity. Scratch marks *(excoriations*), skin thickening (*lichenification*), and visible cutaneous disease support patients' subjective complaints.

To complicate the issue, some patients with typically itchy diseases, such as scabies, deny that they itch. These patients may complain of burning, stinging, tingling, tickling, or a crawling sensation. These symptoms are closely related to pruritus, have similar pathogenic mechanisms, and are treated identically. Bernhard (14) summarized this notion by stating, “one man's itch is another man's tickle . . .and one man's stinging itch is another man's pain.” For most people, itch is readily distinguished from pain, and many patients with severe pruritus would be happy to have pain instead (15).

Pruritus is a distinct, complex sensation that may be considered a primary sensory modality (10). The itch receptor is a dermal, free, nerve arborization that has recently been differentiated from other sensory fibers (15). Although itch fibers are difficult to distinguish from the pain receptor histologically, they may be distinguished electrophysiologically. Unmyelinated C fibers carry pruritus sensations to the thalamus and subthalamus via the spinal cord. Experimental injection of histamine into the skin induces itch or pain. This histamine-induced pruritus may be suppressed by systemic antihistamine administration (16). Because many patients with pruritus show no signs of histamine release (e.g., cutaneous wheal and flare), it is likely that other compounds (e.g., cytokines and neuropeptides) cause most pruritus. Furthermore, the failure of many pruritic conditions to improve with nonsedating antihistamines suggests that histamine is a minor pruritus mediator (17,18). Studies have revealed that pruritus may be caused by opiates, serotonin and other neuropeptides, prostaglandins, kinins, proteases, and physical stimuli (10). Each of these agents may induce pruritus primarily or act via secondary mediators.

The sensation of pruritus also may arise within the central nervous system. Systemic opioids are known to induce pruritus, and the opioid-antagonists, including naloxone hydrochloride, naltrexone hydrochloride, and nalmefine hydrochloride, decrease the pruritus of cholestatic and other liver disease (19,20,21 and 22). Exogenous opioids administered in small quantities to spinal levels in spinal anesthesia relieve pain and can stimulate itch (23). Plasma from patients with cholestatic itching cause facial scratching when introduced into the medullary dorsal horn of monkeys; this scratching is abolished by administering the opioid receptor antagonist naloxone hydrochloride (24). Although opioids may promote histamine release by mast cells (e.g., exacerbating urticarial itch), opioid peptides generally do not cause any release of histamine when injected alone.

Other central nervous system pruritic phenomena include cerebrovascular accident pruritus (25) and phantom limb or phantom breast pruritus (i.e., pruritus in an amputated extremity or removed breast) (26,27). Thus, it is clear that pruritus is often not histamine induced and may not arise in the skin.

DERMATOLOGICAL DISEASES AND PRURITUS

Many skin diseases may contribute to the sensation of pruritus. Dry skin, or *xerosis*, is commonly seen in cancer patients who have generalized wasting or who have undergone chemotherapy or radiation therapy. Xerosis makes the skin more susceptible to irritation from environmental assault (28).

Many other diseases may present with pruritus, including scabies, atopic dermatitis, dermatitis herpetiformis, bullous pemphigoid, miliaria, pediculosis, and urticaria (29). These cutaneous diseases often are readily diagnosed by careful clinical examination. Signs of dermatological diseases may be remarkably subtle or nonspecific in any given patient, particularly in the immunocompromised host. There is no substitute for an excellent physical examination of the skin surface (30,31,32,33,34,35 and 36).

PRURITUS AND MALIGNANCY

Pruritus may be associated with virtually any malignancy (Table 20-1) (37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52 and 53). Some neoplasms are more frequently associated with pruritus. Primary polycythemia, for example, has a pruritus prevalence of 30–50%, and Hodgkin's disease has a prevalence of 15%. Cutaneous T-cell lymphoma, peripheral T-cell lymphoma, and other cutaneous lymphomas are notoriously pruritic. Generally, the etiology of the pruritus in these patients is a poorly understood paraneoplastic phenomenon. The presence of severe pruritus may be more troublesome than from a symptomcontrol perspective alone. Gobbi and colleagues (48) reported that severe pruritus in Hodgkin's disease predicts a poor prognosis. Pruritus may also be a sign of malignant physical obstruction of the biliary system (51).

TABLE 20-1. SYSTEMIC CONDITIONS REPORTED ASSOCIATED WITH GENERALIZED PRURITUS

PRURITUS AND NONMALIGNANT INTERNAL DISEASES

Cancer patients are not exempt from having concurrent medical conditions. There is no question that other internal diseases may be associated with pruritus. Pruritus has been reported to herald the onset of thyroid disease (54), renal insufficiency (55), liver disease (56), iron deficiency (57), diabetes mellitus (58), paraproteinemia (59), Sjögren syndrome (60), and other conditions. Cancer patients can independently develop other medical conditions, or the cancer itself may cause a systemic condition, such as biliary obstruction, that may cause pruritus. Mechanisms of pruritus induction in most of these diseases are poorly understood. It has been postulated that renal disease may induce a metastatic calcification, hyperphosphatemia, xerosis, mast cell proliferation, and other changes that might be associated with pruritus.

CANCER THERAPY

Pruritus may be the result of a chemotherapy reaction, radiation therapy, or medications used for symptom management. Pruritus has been reported as an adverse reaction to chemotherapeutic agents, including those listed in Table 20-2 (61,62,63,64,65 and 66). New combinations of chemotherapeutic agents in ever increasing dosage regimens undoubtedly will be associated with increased cutaneous toxicity.

Bacille Calmette-Guérin
Bleomycin sulfate
Carboplatin
Carmustine
Chlorambucil
Cisplatin
Cyclophosphamide
Cytosine arabinoside and daunomycin
Daunomycin
Docetaxel
Doxorubicin
Gemcitabine hydrochloride
Hydroxyurea
Interleukin-2 with levamisole hydrochloride or alpha interferon
L-Asparaginase
Mechlorethamine hydrochloride
Megestrol acetate
Methotrexate
Mitomycin
Paclitaxel
Procarbazine hydrochloride

TABLE 20-2. ANTITUMOR AGENTS ASSOCIATED WITH PRURITUS

Acute radiodermatitis may cause erythema and pruritus. Additionally, chronic radiodermatitis can be associated with severe xerosis, skin thinning, and ease of irritation. Total body electron beam radiation may make the entire skin surface dry and pruritic.

All clinicians managing cancer patients are familiar with the typical morbilliform drug rash from antibiotics and other supportive agents. Similar to this eruption is the engraftment phenomenon in bone marrow transplant recipients; however, many pruritogenic drugs do not induce any rash. As stated, opiates may induce pruritus via central nervous mechanisms. Others, such as estrogens or ketoconazole, may precipitate cholestatis and thus induce pruritus. It is noteworthy that placebo agents may induce pruritus in as many as 5% of the people treated. More than 100 medications are reported to cause pruritus without a rash (62). Careful review of the medication history and simplification of the drug regimen is essential.

NEUROPSYCHIATRIC DISEASE AND PRURITIS

Calnan and O'Neill (67) found that in most patients with a chief complaint of generalized pruritus, the itch began at a time of emotional stress. Edwards and colleagues (68) later reported that a high level of psychological stress enhances a person's ability to perceive intense itch stimuli. In cancer patients, psychological stress, depression, anxiety, and organic brain diseases undoubtedly contribute to cutaneous diseases (69,70 and 71). Recognition of neuropsychiatric disease may lead to better control.

EVALUATION OF THE PRURITIC PATIENT

Obtaining a focused history, a directed review of symptoms, and a focused clinical examination may lead to a clinical diagnosis. The physician first should probe for likely pharmaceutical agents that could exacerbate pruritus. A temporal history of therapeutic agent initiation within 2 weeks of the onset of pruritus may be helpful. Other historic points of value include an abnormal or excessive bathing history, others in the family or household with similar problems, and symptoms of neuropsychiatric disease. Complete dermatological clinical examination quickly excludes urticaria, scabies, and a host of other dermatological diagnoses.

Some patients with long-standing, generalized pruritus may require further evaluation. For practicing dermatological clinicians, further investigation may be warranted. This evaluation should include a careful history, physical examination, and appropriate, limited, screening laboratory tests. Extensive, undirected evaluation of these patients rarely leads to a specific attributable cause (72).

There is no single list, nor are there specific guidelines for tests that must be performed in any individual patient. Scabies preparations, fungal examinations, and skin biopsies may be needed to diagnose specific dermatological diseases.

TOPICAL TREATMENT

Ideally, the physician would choose the single topical medication that corrects the underlying condition. Although this scenario occasionally occurs (e.g., permethrin for scabies infestation), symptomatic treatment is less specific. Therefore, the clinician must use all diagnostic skills to provide the patient with reasonable relief. Table 20-3 presents the advantages and disadvantages of different topical agents.

Topical agent	Examples	Advantages	Disadvantages
Emollients and moisturizers	Petrolatum moisturizing lotions	Inexpensive, reduces irritant dermatitis	May be too greasy, insufficient in inflammatory diseases
Corticosteroids	Hydrocortisone	Effective for inflammatory dermatoses, mainstay of topical therapy	May cause atrophy, sensitivity, adrenal suppression
	Desoxide	—	—
	Triamcinolone	—	—
	Fluocinonide	—	—
	Halobetasol	—	—
Topical immunomodulators	Tacrolimus	Effective for inflammatory dermatoses, no atrophy	May cause burning on application
Anesthetics	Camphor	Excellent pruritus relief, no atrophy or adrenal suppression	Potentially sensitizing
	Pramoxine	—	—
	Benzocaine	—	—
	Prilocaine (EMLA)	—	—
	Menthol	—	—
Antihistamines	Diphenhydramine hydrochloride	Modest relief, no atrophy or adrenal suppression	Potentially sedating and sensitizing
	Doxepin hydrochloride	—	—
Cooling agents	Calamine	May be soothing and cooling	Calamine leaves visible film
	Alcohol	—	Alcohol dries the skin
Miscellaneous	Coal tar	Coal tar is anti-inflammatory	Tar is not elegant and stains
	Capsaicin	Capsaicin works differently than other agents	Capsaicin often burns

TABLE 20-3. ADVANTAGES AND DISADVANTAGES OF TOPICAL AGENTS

One of the most important aspects of skin therapy that must be addressed is hydration and lubrication of the skin surface (28,73). A simple but sometimes effective therapeutic approach is to apply emollients (lotions, creams, and ointments) on the dry skin twice daily. Emollients with camphor and menthol (e.g., Sarna lotion), phenol, pramoxine (PrameGel, Pramosone, or Aveeno anti-itch lotion) or benzocaine (Lanacane) may provide relief. Camphor, phenol, menthol, pramoxine, and benzocaine have local anesthetic effects (12).

Age-old remedies such as cool compresses (application of a wet washcloth for 20 minutes) and shake lotions (calamine) may prove highly efficacious. Cooling the skin

may provide remarkable pruritus relief. Oatmeal baths (Aveeno) or baths in therapeutic salts may also provide short-term symptomatic relief.

Topical corticosteroids may be useful adjunctive agents for pruritus control. When used properly, they should be prescribed in amounts necessary to cover the affected skin. Table 20-4 provides prescribing quantity information. Although any topical corticosteroid may be useful in a given patient, for widespread pruritus, hydrocortisone (1% or 2.5%) or triamcinolone (0.1%) preparations are generally effective. Because of the relatively thin skin of some cancer patients, long-term use of halogenated corticosteroids should be approached with great caution. Overuse of corticosteroids in unsupervised or overzealous patients is a common cause of dermatological iatrogenic disease (74). Even when topical corticosteroids are required, the use of emollients remains indicated (75,76).

Location	One application (g)	Twice daily for 1 wk[a]	Twice daily for 1 mo[a]
Hands, scalp, genitalia, or face	2	30 g (1 oz)	120 g (4 oz)
Upper extremity or one side of trunk	3	45 g (1.5 oz)	180 g (6 oz)
One lower extremity	4	60 g (2 oz)	240 g (8 oz)
Entire body	30–60	540 g (1 lb)	2700 g (5 lb)

[a]Although the twice-daily dosing of corticosteroid agents is appropriate for many patients, clinicians employ these agents from daily to four times daily.

TABLE 20-4. AMOUNTS OF TOPICAL CORTICOSTEROID AGENT PRESCRIBING INFORMATION

Topical tacrolimus (Protopic) 0.1% ointment is also an effective anti-inflammatory product for itching. It may cause some burning and stinging on topical application, but can be used for long periods of time on any skin site without risk of atrophy (77,78). Although success has been demonstrated only with atopic dermatitis, it is likely to be effective for a broad range of diseases that involve cutaneous inflammation.

Capsaicin cream (Zostrix) is of limited help in selected patients with a wide range of inflammatory and noninflammatory dermatoses (79,80 and 81). Topical capsaicin should be applied three times daily and may be used indefinitely. Its application requires careful patient instruction, as it often initially produces burning or stinging sensations or superficial burns. In many cases, after 1 or more weeks, the burning sensation diminishes and relief from pruritus follows. Capsaicin is not appropriate for generalized pruritus because of its significant expense and irritation potential.

Other agents have modest topical efficacy in relieving pruritus. The eutectic mixture of local anesthetics lidocaine and prilocaine (EMLA) has been demonstrated to be helpful in experimentally induced pruritus (82) and may prove useful in recalcitrant pruritic conditions. However, it is likely to offer no additional advantages over other anesthetics mentioned. Topical doxepin hydrochloride (Zonalon), an antidepressant and antihistamine, is a useful noncorticosteroid pruritus medication with modest demonstrated efficacy (83). Topical doxepin hydrochloride may cause sedation and is particularly likely to cause allergic contact dermatitis. Clinicians should be aware that all topical agents, including emollients, corticosteroids, antihistamines, and anesthetics, have sensitizing potential and may induce allergic contact dermatitis.

ORAL TREATMENT

In patients with pruritus that interferes with sleep or pruritus that may have a significant neuropsychiatric component, oral antipruritic agents may prove important in symptomatic relief. Antihistamines, such as hydroxyzine (Atarax) and diphenhydramine hydrochloride (Benadryl), not only are occasionally antipruritic but also have important central nervous system effects. In a review of the pharmacological control of pruritus from nearly two decades ago, Winkelmann (84) stated that the most effective antihistamines have central nervous system effects. Moreover, ensuring adequate sedation can be important now that there is good evidence that pruritus disturbs normal sleep (85). However, some patients, especially the elderly, may have increased sensitivity to antihistamines, and memory impairment or impaired psychomotor function may result from their administration (3,4). Cetirizine hydrochloride (Zyrtek) is an antihistamine that is less sedating than hydroxyzine, but more sedating than the typically nonsedating antihistamines (e.g., loratidine and fexofenadine hydrochloride).

In conditions other than urticaria, the nonsedating antihistamines may have only marginal therapeutic effect. There are conflicting data on the antipruritic efficacy of terfenadine and acrivastine in atopic dermatitis (18,86). Although they may be useful agents in the treatment of urticaria, nonsedating antihistamines have limited application in nonurticarial conditions. Moreover, the role of histamine in itch mediation in cancer patients is even more questionable. Burtin and colleagues (87) found a decreased skin response to histamine injection in cancer patients. They postulated that the presence of a tumor mimics the effects of general administration of histamine H_1 antagonists on the skin response to histamine.

Doxepin hydrochloride, a tricyclic antidepressant with antihistamine activity (88), may be an effective agent for the treatment of refractory pruritus, but *in vivo* has similar efficacy in suppressing histamine to hydroxyzine.

Systemic corticosteroids for pruritus are often highly effective, but their use can present certain difficulties. All oncologic practitioners are aware that chronic pathological states, including hypertension, diabetes, fluid retention, and osteoporosis, all may be exacerbated by intramuscular or oral corticosteroids. Systemic corticosteroids are particularly effective for brief periods for morbilliform drug eruptions and allergic or irritant contact dermatitis. More prolonged use may induce adverse sequelae.

A variety of other systemic agents have been used with some effect in specific disease states (Table 20-5). Activated charcoal (89), naloxone hydrochloride (19,20), naltrexone hydrochloride (22), and cholestyramine (90), for instance, have been demonstrated to be effective in the pruritus of biliary cirrhosis. Rifampin may be effective for the pruritus of primary biliary cirrhosis (90,91). Aspirin occasionally exacerbates pruritus but has been reported to be helpful in the treatment of pruritus associated with polycythemia rubra vera (50). Interferon-a has been used with some success in intractable pruritic conditions, especially polycythemia vera (52,53), but its cost and side effects demand careful consideration. Although purely anecdotal, our experience with thalidomide, a teratogenic anti-inflammatory agent, suggests that this agent is also extremely useful for intractable pruritus if skin inflammation is present (92).

Disease	Drug or modality	Reference
Renal insufficiency or failure	Ultraviolet B phototherapy	97–99
Hepatic cholestasis	Activated charcoal	89
	Rifampin	90,91
	Ondansetron	91,94
	Cholestyramine	90
	Nalmefine hydrochloride	21,22
Inflammatory skin diseases	Systemic corticosteroids	7–10,12,13
	Topical corticosteroids	7–10,12,13
	Topical tacrolimus	77,78
	Phototherapy	96–99
Urticaria	Antihistamines	13
	Systemic corticosteroids	13

TABLE 20-5. SYSTEMIC OR PHYSICAL MODALITY PRURITUS TREATMENTS FOR SPECIFIC CONDITIONS

The serotonin agents paroxetine hydrochloride (93) and ondansetron (94) have shown some effect with intractable pruritus, but their mechanism of action is unclear. Although these findings are preliminary, the reported efficacy with this class of pharmacological agents represents one of the most important recent advances in pruritus. These agents may have a role to play in the pruritus of liver disease and a wide variety of other conditions.

The reader always should bear in mind that if a patient obtains relief with any given medication, the medication cannot always take credit. In a classic study, Epstein

and Pinski (95) found that placebo therapy provides pruritus relief with a surprisingly high success rate.

PHYSICAL TREATMENT MODALITIES

Ultraviolet A (UVA), ultraviolet B (UVB), and psoralen photochemotherapy have been successfully employed in a wide range of pruritic disorders, from atopic dermatitis to renal disease (96,97 and 98). Because of its high degree of efficacy, UVB has become the treatment of choice for uremic pruritus in some centers, including our own. We administer UVB, combination UVA-UVB, and psoralen photochemotherapy treatments for pruritus. UV doses are usually administered three times weekly in doses (99). UV doses are progressively increased until erythema is attained, then the therapy is individually adjusted to accommodate the patients' photosensitivity. To attain symptomatic relief, 20–30 treatments may be necessary; occasionally, weekly maintenance therapy is continued.

CONCLUSIONS

Pruritus in cancer patients is common and provides a diagnostic and therapeutic challenge for the physician. Evaluation may be limited to obtaining an excellent history and physical examination. Alternatively, an exhaustive search for systemic disease occasionally may be indicated. The physician should address the therapeutic intervention to correct the underlying cutaneous disease. Systemic antipruritics are often beneficial and well tolerated but have wellknown side effects. Above all, diagnosis and therapy should be individualized for the patient.

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21

TREATMENT OF TUMOR-RELATED SKIN DISORDERS

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As the number of patients diagnosed with cancer continues to rise, a concomitant increase in tumor-related skin disor-ders can be expected. Management of these conditions, which can be challenging, is essential to the patient's overall sense of comfort and well-being. In some cases, diagnosis of tumor-related skin disorders may permit early detection of occult malignancy. In this chapter, tumor-associated skin conditions are divided into three groups: (a) generalized eruptions associated with internal malignancy, (b) cancer-related genodermatoses, and (c) incurable nonmelanoma skin cancer. These disorders are reviewed with respect to commonly associated malignancies (Table 21-1). Emphasis is placed on the more common examples of these uncom-mon conditions, and potential management strategies are discussed.

Tumor-associated disorder	Commonly associated cancer
Pruritus	Hodgkin's lymphoma
Leser-Trelat	Gastric adenocarcinoma
Erythema gyratum repens	Lung cancer
Hypertrichosis lanuginosa acquisita	Lung cancer
Necrolytic migratory erythema	Glucagonoma
Paraneoplastic pemphigus	Non-Hodgkin's lymphoma Chronic lymphocytic leukemia
Bazex's syndrome	Aerodigestive tract carcinoma
Acanthosis nigricans	Gastric adenocarcinoma
Dermatomyositis	Ovarian carcinoma
Sweet's syndrome	Leukemia Colorectal carcinoma
Muir-Torre syndrome	Colorectal carcinoma
Cowden's syndrome	Breast carcinoma Thyroid carcinoma
Multiple endocrine neoplasia	Pheochromocytoma Thyroid carcinoma
Peutz-Jeghers syndrome	Colonic adenoma
Nevoid basal cell carcinoma syndrome	Basal cell carcinoma
Xeroderma pigmentosum	Squamous cell carcinoma Melanoma

TABLE 21-1. TUMOR-ASSOCIATED SKIN DISORDERS

GENERALIZED ERUPTIONS ASSOCIATED WITH INTERNAL MALIGNANCY

Pruritus

Pruritus, or itch, is often nonspecific. It is one of the most common complaints in the elderly patient and is usually secondary to xerosis (dry skin, Fig. 21-1B) (1). However, intractable pruritus accompanied by severe excoriations may be an indicator of internal malignancy (1). This type of pruritus is most commonly encountered in Hodgkin's lymphoma but can be observed with any internal malignancy (2). There are often no true primary lesions on examination, but secondary changes, including excoriations and subsequent lichenification and pigmentary alterations, can be significant (Fig. 21-1A). Pruritus has been reported in up to 25% of patients with Hodgkin's disease and may be an indicator of less favorable prognosis when associated with fever or weight loss (2). Pruritus of Hodgkin's disease is described as intense and burning and usually begins on a localized area.

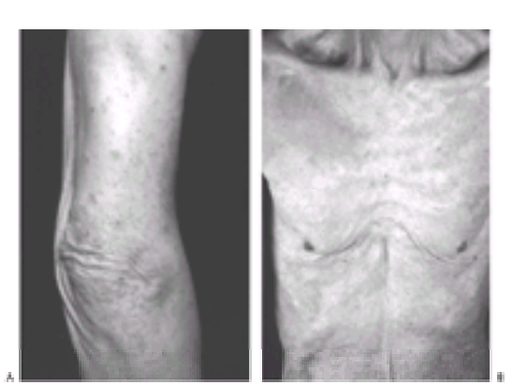

FIGURE 21-1. A: Pruritus in Hodgkin's disease. **B:** Pruritus associated with xerosis. (From NYU Skin & Cancer slide collection, with permission.)

Pruritus also may be a sign of cholestatic liver disease, renal disease, human immunodeficiency virus, thyrotoxicosis, or diabetes (1). Infestation with scabies must also be considered in the differential diagnosis.

In contrast to the nonmalignant associations of localized pruritus, adenocarcinoma and squamous cell carcinoma (SCC) of the brain (3,4), breast (5,6), colon (7,8), pancreas (9), and stomach (10) have been associated with generalized pruritus. Unilateral paroxysmal facial pruritus was reported as a presenting sign in two children with brainstem glioma (3). In both cases, pruritus resolved after radiation therapy for the glioma.

Intractable pruritus is best evaluated by a dermatologist who can distinguish primary pruritus from pruritus secondary to some other cutaneous condition. Work up should include a thorough history and physical examination, including baseline evaluation of complete blood count, liver function tests, and chest x-ray. Skin biopsy of primary lesions (if present) may determine the cause of the pruritus. In addition, age-appropriate and symptom-directed cancer screening should be updated. Treatment options include oral antihistamines (especially sedating antihistamines), topical corticosteroids, and ultraviolet light therapy.

Sign of Leser-Trelat

The sign of Leser-Trelat is defined as the sudden appearance of numerous seborrheic keratoses in association with internal malignancy. It has been most commonly associated with gastric carcinoma (11,12). The sign has been attributed separately to Edmund Leser and Ulysse Trelat (12,13). Interestingly this represents a misnomer because both individuals were actually observing cherry hemangiomas. In fact, it was Hollander who first emphasized the association between internal cancer and seborrheic keratoses in 1900 (14). Little is known about the pathogenesis of Leser-Trelat; however, some investigators point toward increases in tumor-derived growth factors (15).

Seborrheic keratoses are benign lesions and are best described as waxy, hyperpigmented papules or plaques (Fig. 21-2). They appear to be “stuck on” and look as though they might be easily peeled away from the surface of the skin. They are extremely common in older individuals and represent no danger to patients. The differential diagnosis may include benign, premalignant, and malignant lesions including lentigines, nevi, actinic keratoses, atypical nevi, pigmented Bowen's disease, and melanoma. Diagnosis can be confirmed by simple skin biopsy performed by a dermatologist. Leser-Trelat is characterized by the sudden eruption of multiple seborrheic keratoses and most commonly affects the back and chest, although the extremities, groin, and even the face may be affected (12). It must be emphasized that although seborrheic keratoses are common, the sudden appearance of numerous lesions or their appearance before the third decade is not common and should prompt further investigation. Vielhauer et al. report the diagnosis of occult renal cell carcinoma in a patient with Leser-Trelat (11). Curative nephrectomy was performed as a result of early diagnosis.

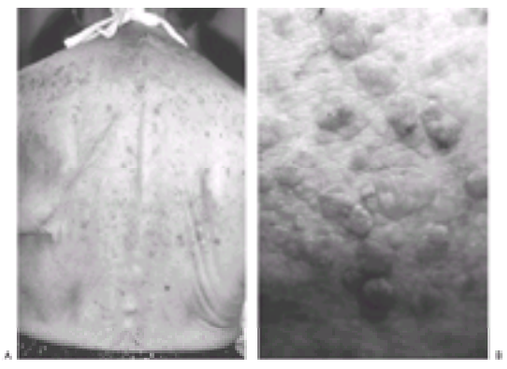

FIGURE 21-2. A: Leser-Trelat associated with lung cancer—note pneumonectomy scar. **B:** Close-up view of seborrheic keratoses in Leser-Trelat. (From Yale Dermatology Residents' slide collection, with permission.)

Further investigation in patients with Leser-Trelat should include a complete history and physical examination, accompanied by routine blood studies including complete blood count, LFTs, chest x-ray, mammogram, and Pap smear for women or prostate-specific antigen test for men. Endoscopic evaluation of the colon should also be considered, as should any symptom-directed diagnostic studies.

The presence of the seborrheic keratoses themselves is not dangerous to the patient, and reassurance of this is necessary. If desired, the keratoses may be removed by curettage under local anesthesia with little risk of scarring. Other treatment methods include cryosurgery with liquid nitrogen and chemical cauterization with topical application of trichloroacetic acid.

Erythema Gyratum Repens

Erythema gyratum repens is part of the group of gyrate erythemas (16). These are reactive, inflammatory dermatoses that share morphologic characteristics and have been described as “figurate,” “ploycyclic,” and “serpiginous” in appearance (16,17). None of the gyrate erythemas has the characteristic appearance of erythema gyratum repens.

Erythema gyratum repens was first described in 1952 by Gamel, who reported it in association with breast carcinoma (18). Since that time, the overwhelming majority of cases have been associated with internal malignancy (16).

On clinical examination, there are serpiginous, erythematous bands that take on a “wood grain” or “zebra-like” appearance (Fig. 21-3). There is usually scaling associated with the lesions and there are often multiple bands. Lesions may be indurated and are likely to migrate over the course of hours. There may be associated pruritus. Unlike the characteristic clinical picture, histopathologic findings are nonspecific and may include hyperkeratosis, acanthosis, spongiosis, and a superficial perivascular lymphohistiocytic infiltrate (16).

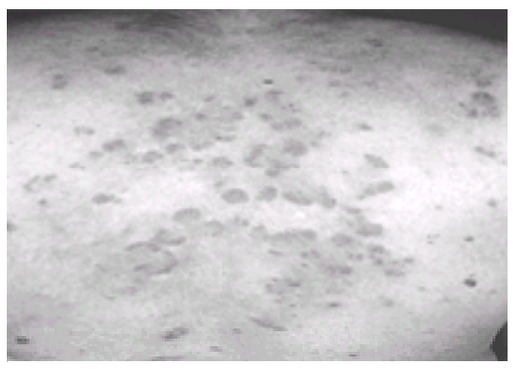

FIGURE 21-3. Erythema gyratum repens in a patient with lung cancer. (From NYU Skin & Cancer slide collection, with permission.)

Suspicion for erythema gyratum repens should result in a dermatological consultation for confirmation. Due to the likelihood of association with internal malignancy, screening for internal malignancy should be performed. Standard screening laboratory and imaging studies should be performed, with special attention toward ruling out cancer of the lung (19). Although most commonly associated with lung cancer (20), erythema gyratum has been reported with breast and renal cancer (18,21) and, in rare cases, in the absence of malignancy (22,23 and 24). It is especially important to repeat screening tests periodically because the eruption may precede the onset of malignancy (16,19).

The most effective treatment is removal of the underlying tumor (16,19). Skin manifestations have resolved after removal of localized tumors and may persist until death in the face of widespread disease. Associated pruritus and inflammation may be relieved with oral antihistamines in combination with midpotency topical corticosteroids.

Hypertrichosis Lanuginosa Acquisita

Hypertrichosis lanuginosa acquisita, also referred to as *malignant dow*n, is characterized by the growth of fine, nonpigmented hair that occurs primarily on the face (25,26). It is most commonly associated with small cell and non–small cell carcinoma of the lung (27) and colorectal cancer (28,29) and has been reported with

carcinomas of the kidney (30), pancreas (31), and in metastatic melanoma (32). It has also been associated with other conditions, among them shock, thyrotoxicosis, porphyria, and ingestion of drugs, including cyclosporine, streptomycin sulfate, phenytoin, spironolactone, diazoxide, minoxidil, interferon, and corticosteroids (25,26).

The most effective treatment for malignant down is that which successfully treats the underlying tumor. Management of cosmesis may be attempted through electrolysis, depilatories, or shaving. Because the hairs are not pigmented, treatment with hair removal laser would likely be unsuccessful, as lasers target melanin in the hair follicle. Treatment with eflornithine hydrochloride cream (13.9%) applied to the affected area twice daily may be successful. This agent inhibits ornithine decarboxylase, a key hair cycle enzyme, and may result in noticeably diminished hair growth (33). The presence of hypertrichosis lanuginosa implies poor prognosis and a survival time of less than 2 years in most patients (25,26,32).

Necrolytic Migratory Erythema

Necrolytic migratory erythema refers to cutaneous manifestations of the glucogonoma syndrome caused by a tumor of the pancreatic islet a-cells (25,34,35). The eruption begins as an erythematous patch involving the groin that spreads to the buttocks, perineum, thighs, and extremities (Fig. 21-4).

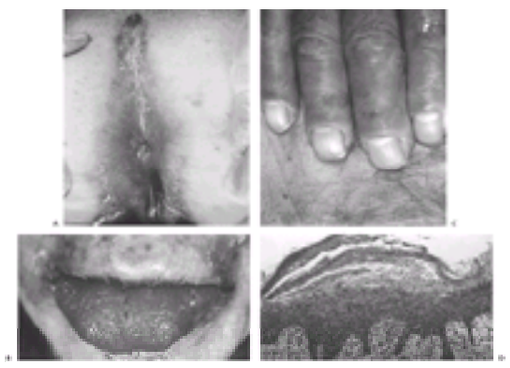

FIGURE 21-4. Necrolytic migratory erythema in the glucagonoma syndrome. **A:** Perianal blistering. **B:** Stomatitis. **C:** Characteristic periungal involvement. **D:** Histologic findings include superficial epidermal necrosis and dyskeratotic cells. (From NYU Skin & Cancer slide collection, with permission.)

The erythematous areas eventually undergo scaling and blister formation. Erosions occur subsequent to rupture of blisters, and healing with induration and pigmentary change follows over the course of several weeks. This may follow a relapsing and remitting course and may be associated with stomatitis. The differential diagnosis includes intertrigo, superficial candidiasis, bullous drug eruption, and pemphigus (25,34,35). Histologic findings include dyskeratotic epidermal cells with superficial epidermal necrosis (Fig. 21-4D) (25,34,35). Elevated plasma glucagon levels are considered diagnostic. Dermatological consultation should be sought to confirm the diagnosis as well as to rule out other skin disorders that may mimic necrolytic migratory erythema. As with other paraneoplastic syndromes, effective tumor therapy results in improvement of cutaneous symptoms (36). Unfortunately, patients with necrolytic migratory erythema may have metastatic disease at presentation. There have been reports of successful treatment using the somatostatin analog octreotide acetate. Jockenhovel et al. reported temporary resolution of cutaneous symptoms with octreotide acetate but noted that the drug had no effect on tumor growth (37). Resolution may be noted as early as 1 week after beginning therapy, but resistance can develop. Shepherd et al. reported successful treatment of cutaneous symptoms with intravenous amino acids (38). While waiting for response, denuded areas should be gently cleansed twice daily, covered with a bland emollient, and dressed with a nonstick bandage. Appropriate monitoring for secondary infection is indicated and is especially important in the hospitalized patient. Interestingly, one of the originally described patients was recently reported as a long-term survivor 24 years after diagnosis (39).

Paraneoplastic Pemphigus

Pemphigus is an immunologically mediated blistering disorder of the skin (40). The three main subtypes, based on target antigens, include pemphigus vulgaris, pemphigus foliaceus (including fogo salvagum, an endemic form), and paraneoplastic pemphigus (PNP). PNP is characterized by severe stomatitis, oral ulcers, and skin lesions with variable morphology (41,42 and 43). It is characteristically associated with hematological malignancies, especially non-Hodgkin's lymphoma and chronic lymphocytic leukemia (42). It has also been associated with spindle cell sarcoma, Waldenstrom's macroglobulinemia, thymoma (malignant and benign), Castleman's tumor, and pancreatic carcinoma (42,44,45,46,47 and 48). The pathogenesis centers on production of autoantibodies that attack components of the hemidesmosome and desmosome that function to link the epidermal cells to their basement membrane and to one another (42). Weakening of this scaffolding system renders the epidermal cells more susceptible to shearing forces, resulting in formation of blisters. The blisters rupture and result in erosive stomatitis, oral ulcers, and cutaneous erosions. In PNP there may be autoantibodies that recognize desmoglein 3, desmoglein 1, plakin proteins, and the hemidesmosomal BP230 (BPAg1) antigen (49).

On physical examination, there is erosive stomatitis and ulceration of the oral mucosa (42,43). There may be associated polymorphous skin lesions (Fig. 21-5). The oral lesions are typically painful and interfere with eating. Skin biopsy reveals varied findings (42). Perilesional biopsy reveals suprabasilar acantholysis of oral epithelium or skin epidermis. Necrotic keratinocytes, along with a scant lymphocytic infiltrate, may be observed. Direct immunofluorescence studies may demonstrate deposition of IgG and C3 on epidermal surfaces and variably along the basement membrane (50). Indirect immunofluorescence studies show the presence of antibodies that recognize antigens on monkey esophagus as well as transitional epithelium from rat bladder (50). Immunoprecipitation studies demonstrate the presence of autoantibodies to desmogleins 1 and 3, desmoplakins, or BPAg1 (42). Due to the complex nature of the disease and its diagnosis, the consideration of PNP demands consultation with a dermatologist.

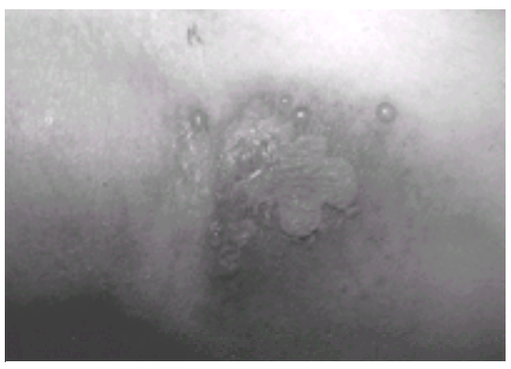

FIGURE 21-5. Paraneoplastic pemphigus. Although paraneoplastic pemphigus commonly affects the oral mucosa, other areas may present with superficial blisters as seen in this patient. (From NYU Skin & Cancer slide collection, with permission.)

Treatment can be difficult. Topical therapy, for the most part, is unrewarding; however, some patients may experience relief with application of high-potency steroid gels to affected oral mucosa on a twice daily basis. Viscous lidocaine generally is of little value, with most patients complaining of burning rather than experiencing relief. Resolution of ulcers has been obtained with administration of cyclosporine (5 mg/kg) in two to three divided daily doses (42). Cyclosporine, a potent immunosuppressive drug, is not without risk of significant side effects, including hypertension and renal compromise, and should only be administered by physicians who are familiar with its use and its side effect profile. Williams et al. report successful treatment of skin and oral lesions in a patient with PNP using mycophenolate mofetil (51). Mycophenolate mofetil is also a potent immunosuppressive agent with side potential effects that include bone marrow suppression.

Bazex's syndrome

Bazex's syndrome, or *acrokeratosis paraneoplastica*, refers to a cutaneous syndrome of psoriasoform lesions on the ears, fingers, and toes, with associated nail changes, that occurs in the context of an internal malignancy (Fig. 21-6) (52). Bazex et al. initially described this in association with carcinoma of the piriform sinus (53). Subsequent reports have described associations primarily with cancers of the aerodigestive tract and carcinomas metastatic to lymph nodes and mediastinum

(52,54,55). In addition, Bazex has been reported with colon (56), bladder (55), and neuroendocrine cancer (57), as well as primary cutaneous SCC (58).

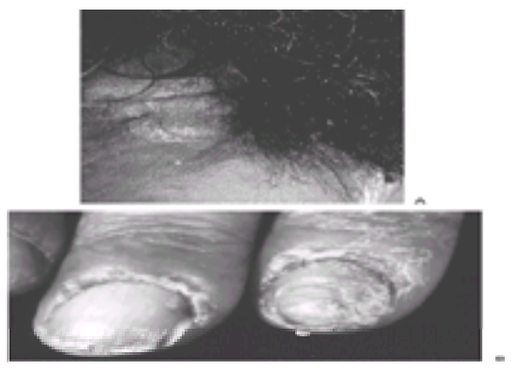

FIGURE 21-6. Bazex's syndrome. **A:** Psoriasoform dermatitis. **B:** Characteristic periungal involvement. (From Yale Dermatology Residents' slide collection, with permission.)

The syndrome may evolve through three stages (52,54,55). In the initial stage, there is vesicle formation with thickening of the periungal skin, subungal hyperkeratosis, and nail dystrophy. Erythematous, scaled plaques develop on the ears, fingers, and toes. The lesions characteristically affect the dorsal aspects of the digits and the helices of the ears. This stage can last anywhere between 2 and 12 months. The second stage ensues if the tumor remains undiagnosed and untreated, and is characterized by progression of skin lesions that are usually refractory to local therapy. With progression comes violaceous color change noted on the palms and soles. If the tumor remains unrecognized, the third stage of Bazex's syndrome is characterized by spread of skin lesions to the trunk, extremities, and scalp.

Histopathologic analysis may reveal foci epidermal cytoplasmic eosinophilia and vacuolization of keratinocytes with pyknosis of their nuclei. A perivascular mixed cell infiltrate may be present in the superficial dermis (52). In one report of Bazex's syndrome associated with SCC of the tonsil, direct immunofluorescence studies showed deposition of IgA, IgM, IgG, and C3 on the basement membrane (59). The authors stated that this supported and immunologically mediated pathogenic mechanism.

Treatment of the tumor can result in resolution of cutaneous symptoms (52,60). This was illustrated in a recent report of Bazex that occurred in association with a primary cutaneous SCC of the lower extremity (58) In that case cutaneous manifestations of Bazex's syndrome resolved after excision of the skin cancer.

Acanthosis Nigricans

Acanthosis nigricans can be associated with internal cancers, particularly gastric adenocarcinoma, as well as endocrinopathies resulting in hyperinsulinemia and insulin resistance (26,61,62). The pathogenesis may lie in the similarity of insulin and insulin-like growth factor (26). Binding of insulin-like growth factor receptors by insulin or by tumorderived growth factors may result in cellular growth and subsequent development of characteristic clinical findings.

On physical examination, velvet-like, hyperpigmented plaques are present on the neck, axilla, inframammary folds, and groin (Fig. 21-7) (62). There may be mucosal thickening as well (63). Microscopic examination shows hyperkeratosis and papillomatosis without epidermal hyperplasia or excess melanin deposition.

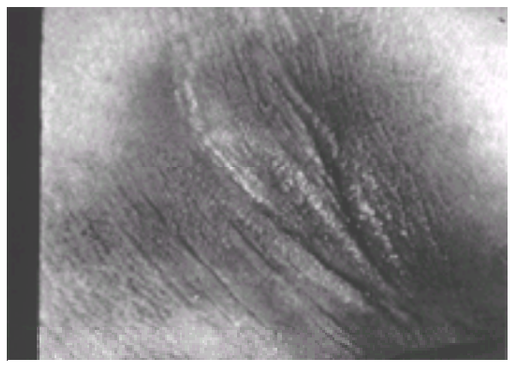

FIGURE 21-7. Acanthosis nigricans. Acanthosis nigricans is characterized by velvety, hyperpigmented plaques involving intertriginous areas. (From Yale Dermatology Residents' slide collection, with permission.)

Acanthosis nigricans is most frequently associated with adenocarcinoma of the stomach (64) but may be associated with almost any internal cancer. Recently, the coexistence of acanthosis nigricans and Leser-Trelat was reported in a patient with advanced gastric adenocarcinoma (15). In that case, appearance of both conditions preceded other manifestations of the malignancy by 6 months. Treatment is difficult even with successful treatment of the underlying cancer.

Dermatomyositis

Dermatomyositis is characterized by proximal muscle weakness in conjunction with characteristic cutaneous findings and may occur in adults in association with any internal cancer (65). The proximal muscle weakness manifests with inability to perform daily activities such as combing hair, putting on or removing a shirt or coat, and rising from a seated position. Cutaneous findings usually involve the periorbital area, chest, back, and fingers.

Cutaneous examination frequently reveals a heliotrope rash, Gottron's papules, and poikiloderma in the shawl distribution (Fig. 21-8) (65). The heliotrope rash is characterized by an erythematous dermatitis involving the periorbital areas of the face. Guttron's papules are characteristic raised lesions present on the extensor aspects of the fingers. The shawl sign refers to poikiloderma (blotchy erythema with telangiectasias, atrophy, and hypopigmentation) involving the upper chest, shoulders, and upper back.

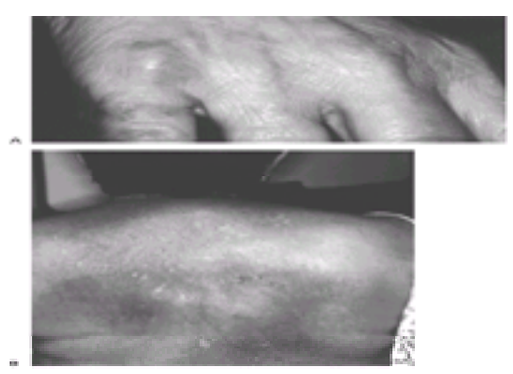

FIGURE 21-8. Dermatomyositis. **A:** Gottron's papule. **B:** Characteristic erythematous dermatitis. (From Yale Dermatology Residents' slide collection, with permission.)

Skin biopsy is remarkable for superficial and deep perivascular infiltrate, and there may be basement membrane thickening as in lupus (65). CPK and aldolase are

elevated in dermatomyositis. Anti-jo-1 antibody and antinuclear antibodies may be present (65). The combination of the characteristic cutaneous findings, proximal muscle weakness, and elevated CPK and aldolase values are diagnostic.

Dermatomyositis may be associated with any malignancy, particularly ovarian cancer (65,66). This is supported by the findings of Cherin et al. (67), who reported ovarian cancer in 21% of their female patients older than 40 years of age with dermatomyositis. This represents a significant increase over the percentage of ovarian carcinoma in the general population (approximately 1%). Dermatomyositis has been reported with B cell lymphoma (68), thymoma (69), colon cancer (70,71), and metastatic melanoma (72). It should be clear that patients with dermatomyositis must be evaluated for the presence of an internal malignancy, with special attention to gynecological cancers.

Sweet's Syndrome

Acute febrile neutrophilic dermatosis was first described by Robert Sweet (73,74). It is characterized by the combination of acute onset of fever, anemia, neutrophilia, and characteristic skin lesions (26,75,76). Skin lesions can be described as erythematous plaques and blisters that involve the face, neck, chest, and extremities (Fig. 21-9). Involvement of the eyes, joints, and oral mucosa, as well as involvement of lung, liver, kidney, and central nervous system, has been described (76).

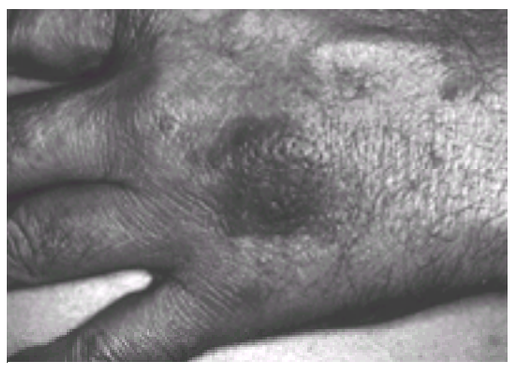

FIGURE 21-9. Sweet's syndrome. An indurated plaque in a patient with Sweet's syndrome in acute myelogenous leukemia. (From NYU Skin & Cancer slide collection, with permission.)

Sweet's syndrome occurs in the context of hematopoietic tumors, especially leukemia, and has been reported with solid malignant tumors (76). It has also been reported with chronic inflammatory disorders (77) and, in rare cases, with pregnancy (78). In one review of 249 cases, it was reported that Sweet's syndrome was associated with hematological malignancies in 40% of cases and with solid tumors in 7% of cases (76). In a study of cases of Sweet's syndrome associated with solid tumors (79), the most commonly associated malignancies were genitourinary carcinomas (37%), breast carcinomas (23%), and cancers of the gastrointestinal tract (17%). Sweet's syndrome responds rapidly to oral corticosteroid therapy (77). Other treatments, including potassium iodide, colchicine, dapsone, clofazimine, and cyclosporine, have been reported (76,77,80).

CANCER-RELATED GENODERMATOSES

Muir-Torre Syndrome

Muir-Torre syndrome (MTS) was first described by Muir et al. in 1967 (81) and by Torre in 1968 (82). It was Torre who noted the association of sebaceous adenomas of the skin and internal cancers. The internal cancers were most commonly low-grade colorectal carcinomas. MTS is transmitted in autosomal dominant fashion (83). The skin lesions most often associated with MTS are sebaceous adenomas, sebaceous epitheliomas, sebaceous carcinomas, and keratoacanthoma (83).

On physical examination, sebaceous adenomas appear as flesh colored to yellow papules, usually measuring less than 5 mm. They are commonly located on the face but can occur anywhere. Sebaceous epitheliomas can take on a cystic appearance, whereas sebaceous carcinomas typically appear as a papule on the eyelid and can be overlooked in the early stages. Sebaceous carcinomas are common on the eyelid but may appear as cystic lesions on the extremities (Fig. 21-10). Keratoacanthomas are a subtype of SCC and usually occur as a rapidly growing nodule with a keratinaceous central core.

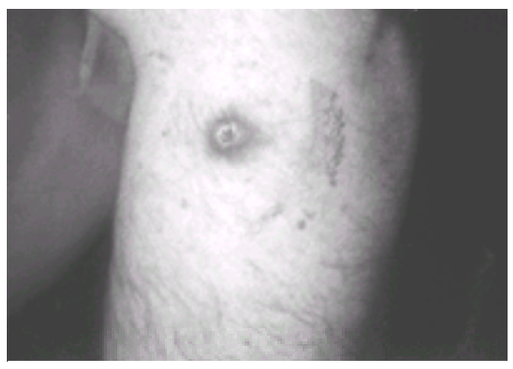

FIGURE 21-10. Muir-Torre Syndrome. A sebaceous carcinoma in a patient with Muir-Torre Syndrome. (Photo by John Carucci, MD, PhD, Weil Medical College of Cornell University.)

The treatment of choice for sebaceous carcinoma and keratoacanthomas like SCC on the face is Mohs' micrographic surgery (MMS) (84). MMS offers the highest rate of cure and the advantage of tissue conservation due to superior margin control. Sebaceous epitheliomas can be excised with clear margins whereas sebaceous adenomas can be removed by tangential (shave) excision. Incomplete removal is likely to result in local recurrence. Management must proceed beyond treatment of the primary skin lesions. MTS is associated with colorectal, genitourinary, and hematological malignancies and appropriate cancer screening must be performed on patients and their family members due to the autosomal dominant mode of inheritance (83).

Cowden's Syndrome

Cowden's syndrome is also known as multiple hamartoma syndrome and facial and oral lesions in association with cancers of the breast and thyroid (85). Multiple hamartoma syndrome is inherited in autosomal dominant fashion, and although only approximately 100 cases have been reported thus far, it may be more common than originally thought (85,86). The usual age of presentation is between 20 and 40 years and the primary mucocutaneous manifestations include facial trichilemmomas and oral papillomas (85,86). Cowden's syndrome is believed to be due to mutations in the PTEN gene (87).

Trichilemmomas appear as tan to yellow verrucous papules on the central face (Fig. 21-11). Oral papillomas give a cobblestone appearance to the tongue and oral mucosa (85). There may be associated acral keratotic papules on the hands and wrists and translucent punctate keratoses on the palms and soles.

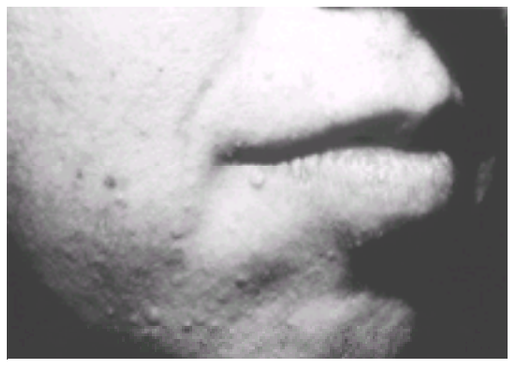

FIGURE 21-11. Cowden's syndrome. Perioral trichilemmomas are characteristic in Cowden's syndrome. (From Yale Dermatology Residents' slide collection, with permission.)

Suspicion for Cowden's syndrome should result in dermatological consultation for confirmation. Appropriate cancer screening should be performed with attention to breast and thyroid carcinomas (88,89 and 90). Trichilemmomas are benign lesions; however, trichilemmomal carcinoma has been reported in Cowden's syndrome (91). Treatment may be attempted by laser ablation, dermabrasion, or shave excision.

Multiple Endocrine Neoplasia

Multiple endocrine neoplasia (MEN IIb) is also known as the *multiple mucosal neuroma syndrome* (92). It is inherited in autosomal dominant fashion due to a mutation on chromosome 10q11.2 but can occur sporadically in up to 50% of cases (92). Patients usually present early and it is key that the appearance of mucosal lesions may precede development of internal cancers by 10 years. It is thought to be due to a mutation in the RET proto-oncogene, which may affect neural crest development (93).

Mucocutaneous signs include neuromas on the tongue, lips, and oral mucosa. These appear as papules or nodules and may involve the palatal, nasal, and laryngeal mucosa (92). Patients with MEN IIb exhibit a marfanoid habitus. Associated internal cancers include pheochromocytoma and medullary carcinoma of the thyroid. Gastrointestinal neuromas may lead to diarrhea, constipation, and megacolon.

If MEN IIb is suspected, consultation with a dermatologist and geneticist is indicated. Patients and family members need to be evaluated for internal malignancies and work up should include urine catecholamine level, thyroid scan, thyroid function tests, and computed tomography scan of the abdomen. Treatment of neuromas by excision often results in recurrence.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) or *periorificial lentiginosis* is characterized by perioral skin lesions in association with colonic polyps that have malignant potential (94,95 and 96). It can be inherited in autosomal dominant fashion or may occur sporadically (94,95 and 96). The pigmented lesions appear around the mouth during the first few years of life and precede the development of colonic polyps by at least 10 years in most cases (94,95 and 96).

The cutaneous lesions are pigmented macules usually measuring between 2 and 5 mm (Fig. 21-12) (94,95 and 96). They are uniformly brown to black in color, symmetrical, and occur in the perioral area, buccal mucosa, palms, soles, and digits.

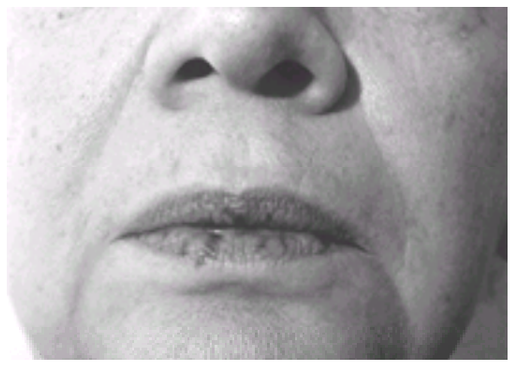

FIGURE 21-12. Peutz-Jeghers syndrome. Labial lentigines in a patient with Peutz-Jeghers syndrome. (From Yale Dermatology Residents' slide collection, with permission.)

Suspicion for PJS should result in consultation with a dermatologist and gastroenterologist. PJS is associated with hamartomas of the colon, which have the potential to develop into adenocarcinoma. There is also increased risk of ovarian, breast, and pancreatic carcinoma. Therefore, adequate periodic screening is essential for patients with PJS.

Lentigines can be treated successfully with the Q-switched ruby laser (693 nm) (97,98 and 99).

INCURABLE NONMELANOMA SKIN CANCER

The incidence of nonmelanoma skin cancer (NMSC) continues to rise, with over 1.2 million cases reported in the United States last year (100). The majority of these (75%) were basal cell carcinomas (BCCs), the most common human cancer. The majority of the remaining 25% (>200,000) were primary cutaneous SCC. In most instances, these cancers are curable through office-based dermatological surgical procedures (101). The highest cure rates (99% for primary cutaneous carcinomas) and greatest conservation of normal tissue are offered by MMS (102). Other procedures, including standard excision, curettage and desiccation (C&D), and ablation by other methods have also proven successful (101). However, there exists a small subset of patients for whom the overall prognosis is not as favorable, and in whom NMSC may in fact be incurable. These include patients with inherited syndromes such as nevoid basal cell carcinoma syndrome (NBCCS) and xeroderma pigmentosum (XP).

Nevoid Basal Cell Carcinoma Syndrome

NBCCS is an inherited (autosomal dominant) condition characterized by predisposition for development of hundreds of BCCs in conjunction with findings that may include borderline intelligence, broad nasal root, palmar pits, and odontogenic cysts (103,104). The syndrome occurs because of defects in the PTCH regulatory gene (105). Mutations in PTCH are found in sporadic BCC as well as in NBCCS.

On physical examination, patients may present with hundreds of BCCs, mostly appearing as superficial erosions (106). Although usually small, lesions may become large over time if neglected (Fig. 21-13). It is likely that palmar pits represent small BCCs as well. The presence and severity of other physical findings may vary. Treatment of vast numbers of BCCs in a single patient presents a therapeutic challenge and requires the use of numerous methods including MMS, excisional surgery, destructive therapy such as C&D and cryotherapy, and treatment with topically applied agents including 5-fluorouracil (5-FU) and imiquimod.

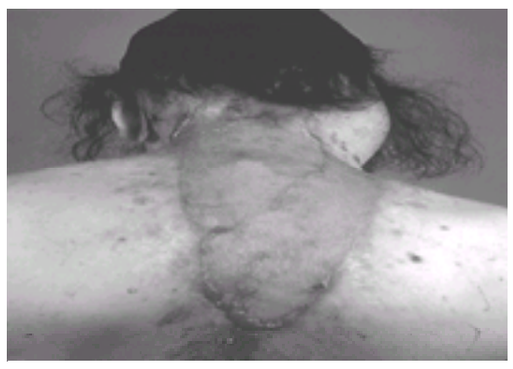

FIGURE 21-13. Nevoid basal cell carcinoma syndrome. Long-neglected, superficial basal cell carcinoma in a patient with nevoid basal cell carcinoma syndrome. (From NYU Skin & Cancer slide collection, with permission.)

Mohs' Micrographic Surgery

MMS offers the highest cure rates, along with the highest rate of tissue conservation (107). The principles of MMS have been reviewed extensively (84,107). In brief, MMS is performed by specially trained dermatological surgeons in an outpatient setting under local anesthesia. The clinical extent of skin cancer is assessed by curettage followed by removal of the lesion and a 1-mm margin of clinically normal skin. The specimen is mapped precisely and processed immediately under direction of the Mohs' surgeon. Slides are then interpreted by the Mohs' surgeon and any remaining areas of tumor positivity are removed in directed fashion in subsequent stages. After complete removal of the cancer, wound repair options are considered; repairs can be performed with confidence because MMS offers the highest sensitivity in achieving tumor-free margins. In NBCCS, we tend to reserve the use of MMS for high-risk cancers (i.e., skin cancers with aggressive histology or those that occur at high-risk anatomical sites such as the eyelid, nasal tip, or ear).

Excision

Excision of skin cancers offers excellent cure rates when tumor-free margins are achieved. Surgical margins of 4 mm can clear the tumor in 95% of cases (108). However, difficulties arise when performing excisions in NBCCS because there are so many skin cancers that it is difficult to determine where one cancer “ends” and another “begins.” Compounding this is the fact that superficial BCCs are multifocal in nature and tumor-free margins may be more difficult to obtain by conventional excision. We have found that tangential excision followed by gentle cautery is useful in the management of the majority of superficial BCCs encountered in NBCCS.

Destruction of Tumors

Superficial BCCs can be managed by destructive techniques, including C&D and cryosurgery. C&D is performed in three cycles of curettage followed by electrodesiccation (109). Although effective in the management of superficial skin cancers on the trunk and extremities (109), the potential drawbacks include a risk of hypertrophic scarring, along with a lack of histologic confirmation of negative margins.

Cryosurgery is performed by direct application of liquid nitrogen to lesions resulting in a temperature of –50°C (110). Although potentially effective in the management of superficial skin cancers, there are risks of hypopigmentation, hypertrophic scarring, and recurrence due to lack of margin control.

Medical Management

Topical therapies that have been used in superficial skin cancers include 5-FU and imiquimod. Topical 5-FU has been used extensively in the management of actinic keratoses (111) and has been used successfully in combination with cryosurgery for patients with NBCCS (112). Application of 5-FU usually results in a profound inflammatory response that may be disconcerting to the patient if he or she is not adequately prepared.

Imiquimod is a topically applied agent that induces local production of IFN-a (113,114). This, in turn, results in an immunologically mediated inflammatory response that in some cases results in regression of skin cancers (113,114). In pilot studies, it was found that imiquimod was effective in the treatment of superficial BCCs (113,114).

Xeroderma Pigmentosum

XP is an inherited condition characterized by photosensitivity, progressive neurological symptoms, and development of numerous ultraviolet-induced skin cancers that may result in metastasis and death (115,116 and 117). XP is transmitted in autosomal recessive fashion and occurs due to defective DNA excision repair after exposure to ultraviolet radiation (115,116 and 117). Defective postreplication repair occurs in the “XP variant” group (115,116 and 117).

Clinical manifestations appear during infancy and are characterized by severe photosensitivity and sunburn reactions (115,116 and 117). Signs of severe sun damage follow during childhood and include development of lentigines, telangiectasias, and actinic keratoses and skin cancers (Fig. 21-14) (118,119 and 120). The increased risk in development of BCC, SCC, and melanoma is approximately 1000-fold. Management should include aggressive measures to protect patients from the sun. These include limiting outdoor activity to nighttime and using sun protective clothing and sunscreens when traveling during the day.

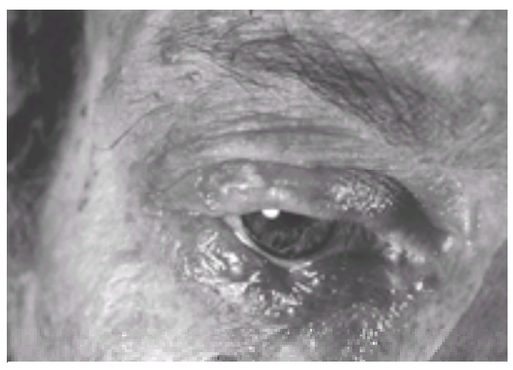

FIGURE 21-14. Xeroderma pigmentosum. Invasive carcinoma involving the lower eyelid in a patient with xeroderma pigmentosum. (From NYU Skin & Cancer slide collection, with permission.)

NMSCs must be managed appropriately by a combination of methods including MMS, excision, or C&D (121). Superficial NMSC and precancerous lesions can be managed topically with 5-FU or imiquimod (113,114,122). Treatment with isotretinoin may be effective in reducing development of SCCs; however, any benefits are lost on discontinuation of therapy (123). Turner et al. report on a patient with XP who was successfully treated for melanoma *in situ* with intralesional interferon (124).

Periodic screening for melanoma is especially important due to the increased risk of XP. Melanoma, if detected, must be managed in standard fashion by excision with appropriate margins based on tumor depth (125).

CONCLUSION

Tumor-associated skin disorders may appear in many forms with varying degrees of severity. In selected cases, prompt diagnosis and effective management can allow for early detection of cancer and alter prognosis. It is therefore essential that any suspected case be evaluated by a dermatologist.

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22

MANAGEMENT OF PRESSURE ULCERS AND FUNGATING WOUNDS

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This chapter presents two skin manifestations—pressure ulcers and fungating wounds—that are commonly seen in the palliative care patient.

PRESSURE ULCERS AND THE ONCOLOGY PATIENT

Pressure ulcers are complex wounds that are defined as lesions caused by unrelieved pressure resulting in damage of underlying tissue (1). Pressure ulcers pose a threat to the patient when immobility, nutritional deficits, advanced age, incontinence, radiation effects, metabolic abnormalities, pain, and persistent or recurrent disease coexist (2). In advanced cancer, clinical conditions such as anorexia-cachexia, malnutrition, anemia, and some metabolic alterations can further affect the skin (3). In the terminally ill, advancing weakness, fatigue, and immobility result in an increased risk of pressure ulcer development (4). Pressure sores can complicate care, increase costs, and more importantly, threaten the quality of life (5). The incidence of pressure ulcers in terminally ill individuals has been reported as ranging from 15–24% (6,7), with an average prevalence of 21% in a hospice setting (8). Given the condition of many advanced cancer patients, these high rates of pressure ulcers are understandable. Although there is extensive literature on pressure ulcers, there are few welldesigned, empirical studies investigating risk, causation, and prevention (9), and fewer still in the palliative care population. This leaves many questions unanswered, and the prevention and management of pressure ulcers remains anecdotal (10). Caregivers and patients must be educated in the current modalities of pressure ulcer prevention and management so that they can decide on the goals of care, and whether the prevention or treatment carries a greater burden than benefits. It should be noted, however, that in certain groups of patients pressure ulcers may develop or worsen despite aggressive preventative or curative treatment. It has been suggested that for patients in the terminal stages of an illness, limited treatment or comfort care and symptom limitation should be the primary goals (11).

ETIOLOGY OF PRESSURE ULCERS

Pressure ulcers develop as a consequence of the occlusion of capillaries from unrelieved external pressure. When pressure is applied from an external surface to a bony prominence (as in the ischial tuberosities when sitting or the coccyx when lying down), the soft tissue is compressed, causing localized ischemia. If the pressure is unrelieved, the capillaries collapse, further disrupting the flow of blood and nutrients. Eventually, hypoxia and edema lead to cellular necrosis (12).

FACTORS THAT INCREASE THE RISK OF PRESSURE ULCER FORMATION

Risk factors may be classified as intrinsic and extrinsic.

Intrinsic Risk Factors

Intrinsic risk factors for pressure ulcer formation include reduced mobility or immobility, sensory impairment, decreased level of consciousness, extremes of age, vascular disease, severe chronic or terminal illness, previous history of pressure damage, malnutrition, and dehydration (13).

Extrinsic Risk Factors

Pressure is the major causative factor in pressure ulcer formation. The pathological effect of excessive pressure on soft tissue can be attributed to the intensity and duration of the pressure and the tolerance of the tissue (the ability to endure pressure without adverse sequelae) (13).

Shearing

Shearing is causative in the creation of pressure ulcers. Shearing occurs when the skin remains stationary and the underlying tissue shifts (e.g., when the head of the bed is raised and the patient slides down toward the foot of the bed). The loosely attached superficial layer of tissue slides over the well-anchored, deeper tissue through which the blood vessels pass to reach the skin. Vessels may rupture, compress, or become distorted, resulting in deep tissue destruction (14).

Friction

Friction injuries occur when the skin moves across a coarse surface, such as bed linens (12), causing an abrasion of the epidermis and the dermis. This makes these tissues generally less tolerant of pressure and shear and provides a potential entry route for infective agents (9).

Urinary Incontinence

Urinary incontinence, which allows moisture to remain on the skin, can lead to maceration and excoriation, disrupting the integrity of the skin. Fecal incontinence and

diarrhea positively correlate with the development of pressure ulcers (15).

PRESSURE ULCER PREVENTION

Prevention of pressure ulcers is consistent with the goals of palliative care, which are to provide relief from suffering and improve the quality of life of both patients and their families (16). Chaplin (4), however, suggests that the comfort of the patient, along with the need to ensure quality of life for the patient and family, must be maintained at all times and may take precedence over the prevention of pressure ulcers. Therefore, pressure ulcers are not always preventable in those who are dying, and comfort may be more important to the patient and family.

If prevention is the choice of the patient and family, efforts begin with control or management of pressure ulcer etiology along with contributing factors. Pressure reduction (especially over bony prominences), keeping the skin clean and as free as possible from contamination by urine or feces, frequent turning, promotion of adequate hydration, and correction of nutritional deficiencies, along with providing active and passive motion, are all helpful strategies. Educating the patient and family regarding the need for a prevention program has been suggested as a preventive strategy for pressure sores in hospice patients (14). The Agency for Health Care Policy and Research (AHCPR) (1) developed guidelines for both the prevention and treatment of pressure ulcers. These guidelines were developed by independent, multidisciplinary panels of private-sector clinicians and other experts convened by the AHCPR to review the research and grade the evidence. In the absence of research, most of the guideline recommendations were made by expert opinion and panel consensus. The prevention guidelines have four components: risk assessment, skin care and early treatment, mechanical loading and support surfaces, and education (13). A comprehensive plan for pressure ulcer prevention is included in Table 22-1 (1). The risk for acquiring a pressure ulcer must be calculated on an ongoing basis and whenever the condition of the patient changes.

Activity or mobility deficit: bedbound patients
Reposition at least every 2 h.
Use pillows or foam wedges to keep bony prominences from direct contact.
Use devices that totally relieve pressure on the heels.
Decrease skin injury caused by friction and shear forces with proper positioning, transferring, and turning techniques.
Use devices that totally relieve pressure on the heels.
Avoid positioning directly on the trochanter.
Elevate the head of the bed as little and for as short a time as possible.
Use lifting devices to move rather than drag patients during transfers and position changes.
Place at-risk patients on a pressure-reducing mattress.
Do not use a donut-type device.
Activity or mobility deficit: chairbound patients
Reposition at least every h.
Have the patient shift weight every 15 min if able.
Use pressure-reducing devices for seating surfaces. Do not use donut-type devices.
Consider postural alignment, distribution of weight, balance, and stability, and pressure relief when positioning patients in chairs or wheelchairs.

TABLE 22-1. EARLY INTERVENTIONS

Risk Assessment/Identification of Patients at Risk

Clinicians are encouraged to select and use a method of risk assessment that ensures systematic evaluation of individual risk factors. Many risk assessment tools exist, but only the Braden Scale (17) and the Norton Scale (18) have been tested extensively. Risk should be reassessed periodically. Care should be modified according to the level of risk (25). Frequency of reassessment usually depends on patient status and institutional policy.

Pressure/Support Surfaces

The reduction or elimination of interface pressures involves the use of support surfaces. There are a variety of support surfaces available, but few clinical trials exist that evaluate these surfaces in terms of outcomes (19). Several factors are involved in the selection of a support surface for the individual patient. The AHCPR guidelines state that a static support surface can be used if a patient can assume a variety of positions without bearing weight on a pressure ulcer.

Moisture/Incontinence

1. Cleanse skin at time of soiling.
2. Minimize skin exposure to moisture. Assess and treat urinary incontinence. When moisture cannot be controlled use products that shield the skin from effluent, and use underpads or briefs that are absorbent and present a quick-drying surface to the skin.

Nutritional Deficits

1. Investigate factors that compromise patient's dietary intake (especially protein or calories) and offer support with eating.
2. 2. Plan and implement a nutritional support or supplementation program for nutritionally compromised persons, if it is consistent with the plan of care as agreed by the patient and caregivers.

Cachexia describes a combination of anorexia (loss of appetite), progressive weight loss, weakness, fatigue, malaise, and loss of skeletal muscle and adipose tissue. Patients with cachexia have a disturbed metabolic activity. Anorexia is common with most advanced cancers. Patients with anorexia may also have dysphagia (difficulty swallowing), abnormal taste sensation, depression, shortness of breath, dry mouth, or chronic nausea as contributing factors to anorexia (20). Treatment of depression, shortness of breath, dry mouth, and nausea may improve caloric intake (16). Supplements usually do not alter survival or the nutritional status of patients, and it is unclear whether they provide any symptomatic benefits. Dietary advice and counseling on the need to tailor nutrition to the patient's wishes and the futility of intensive or invasive nutrition are necessary (16).

Documentation

Interventions should be monitored and documented. Specific details are needed on who should provide the care, how often, and the supplies and equipment needed. How the care is to be undertaken should be individualized, written, and readily available. Furthermore, results of the interventions and the care being rendered and adjustment in the interventions as indicated by the outcomes should be documented. To ensure continuity, documentation of the plan of care must be clear, concise, and accessible to every caregiver (12).

MANAGEMENT OF EXISTING PRESSURE ULCERS

The aim of proposed treatment must be considered in the patient with existing pressure ulcers. Healing may not always be a realistic goal, and the priority then becomes patient comfort and the prevention of further complications (5). Care decisions taken must be discussed by the team providing care and documented with a clear rationale for the decisions reached (4). For example, if pain precludes turning and repositioning or even placement on a support surface, documentation of this agreement and knowledge of its consequences must be carried out. Early treatments of pressure ulcers are listed in Table 22-2.

Skin care and early treatment guidelines
Inspect skin at least once a day. Individualize bathing schedule, avoid hot water, and use a mild cleansing agent.
Minimize environmental factors, such as low humidity and cold air. Use moisturizers for dry skin.
Avoid massage over bony prominences.
Use proper positioning, transferring, and turning techniques.
Use lubricants to reduce friction injuries.
Institute a rehabilitation program.
Monitor and document interventions and outcomes.

TABLE 22-2. EARLY TREATMENTS

PRINCIPLES OF WOUND MANAGEMENT

Elimination or Reduction of Causative Factors

The main cause of a pressure ulcer is pressure; however, malnutrition, incontinence, friction, and shearing, if present, must be managed to facilitate wound healing (21). Assessment for these conditions (Table 22-3) is necessary; if present, interventions such as the following may be needed:

Eliminate/ reduce cause and contributing factors	Provide systemic support	Topical therapy: remove impediments to healing
Pressure Moisture Friction Shear	Assess and monitor patient's overall condition	Necrosis Infection Excess exudate Retain moisture and heat

TABLE 22-3. PRINCIPLES OF WOUND MANAGEMENT: PRESSURE ULCERS

1. Implementation of a turning/repositioning schedule if pressure appears to be the main cause.
2. Use of appropriate measures to reduce friction and shearing (e.g., trapeze, turning sheet, socks, use of knee gatch when head of bed is elevated).
3. Selection of a support surface that can deal with pressure, moisture, friction, or shearing.
4. Management of incontinence with external collection devices, bowel training, prompted voiding.

Doughty (21) maintains that failure to address cause will result in a nonhealing wound despite appropriate systemic and topical therapy.

Systemic Support

Optimizing the overall condition of the patient is necessary to facilitate wound healing. Inadequate oxygen and nutrients retard or prolong the wound healing process. Interventions are predicated on findings and may include actions that support tissue oxygenation, control of diabetes, measures to control insufficient dietary intake, the reduction of edema, and restoration of blood flow (21).

Topical Therapy

The purpose of topical therapy is to provide an optimal environment for facilitating wound healing; this begins with the removal of impediments to healing. Necrosis in a pressure ulcer provides a medium for bacteria and also prolongs the inflammatory phase of wound healing. Débridement usually is indicated for the necrotic pressure ulcer. Another impediment to wound healing that prolongs the inflammatory phase is infection. Pressure ulcers should be assessed for any signs of infection and cultured where appropriate. If the infection invades the surrounding tissue, systemic antibiotics should be considered so that blood and tissue antibiotic levels adequate for infection control can be achieved. Excess exudate can macerate surrounding skin and dilute wound healing factors and nutrients at the wound surface. Protection of the wound includes maintaining a moist wound surface, thereby preventing desiccation and enhancing epidermal migration. This also promotes angiogenesis and connective tissue synthesis. Thermal insulation of the wound maintains normal tissue temperature, which improves blood flow to the wound bed and enhances epidermal migration (22). Appropriate topical treatment is directed by these principles (21).

Education

The AHCPR treatment guidelines strongly propose pressure ulcer education not only for health care professionals but also for patients, family, and caregivers. The guidelines themselves can be used to educate colleagues about evidence-based pressure ulcer treatment. These guidelines are being used by many regulatory agencies to survey health care facilities, and Medicare benefits are reimbursed according to these guidelines. In addition, the guidelines have been used as the standard of practice in the courtroom (23).

Patient's Overall Physical and Mental Status

Comorbid illnesses (e.g., peripheral vascular disease or diabetes, immune deficiencies, collagen vascular disease, malignancies, and psychosis) may limit an individual patient's capacity to heal.

Nutritional Status

It must be verified that the patient is eating. The health history should be reviewed for recent weight loss and to determine whether the serum albumin level is below 3.5 g/dl. If intake continues to be inadequate, impractical, or impossible, dietary counseling should be initiated.

Pressure Reduction Needs

All patients with existing pressure ulcers should be assessed to determine their risk for developing additional pressure ulcers. A static support surface can be used if a patient can assume a variety of positions without bearing weight on a pressure ulcer and without “bottoming out.” An overlay mattress can be checked at various anatomical sites while the patient assumes various positions and outstretched hand (palm up) under the overlay below the body part. If there is less than an inch of support material, the support surface has bottomed out. A dynamic support surface is used when the patient cannot assume a variety of positions without bearing weight on a pressure ulcer, if the patient fully compresses the static support surface, or if the ulcer does not show evidence of healing. If the patient has large stage III or IV pressure ulcers on multiple turning surfaces, a low-air-loss bed or an air-fluidized bed may be indicated (23).

Assessment of Existing Ulcers

Assessment of the ulcer is the basis for planning treatment as well as evaluating the effects of interventions (Table 22-2). Establishing a baseline by in-depth assessment also improves communication among caregivers.

Pressure sores exist on a continuum from reddened yet intact skin to open wounds with extensions to underlying muscle and bone (10). Classification systems provide a means of assessing the extent of ulceration directly attributed to pressure, shear, friction, or a combination of these factors, and use of a recognized pressure ulcer classification system is advisable (24).

Stage

Staging or grading is a method for classifying wounds according to the tissue damage observed. Staging of a necrotic-covered wound cannot be confirmed until the wound base is visible. The Wound Ostomy and Continence Nurses Society (WOCN), in conjunction with the National Pressure Ulcer Advisory Panel (NPUAP), has

incorporated a four-stage classification system. It should be noted that although progression through the stages may occur, down-staging or reversal of the staging process cannot occur.

Stage I

Nonblanchable erythema of intact skin is the heralding lesion of skin ulceration. In those patients with darker skin, discoloration of the skin, warmth, edema, induration, or hardness also may be indicators.

Stage II

Partial-thickness skin loss involving the epidermis, dermis, or both, which may also present as a blister, is seen in stage II.

Stage III

Stage III involves full-thickness skin loss involving damage to, or necrosis of, subcutaneous tissue that may extend down to, but not through, underlying fascia. The ulcer presents clinically as a deep crater with or without undermining adjacent tissue.

Stage IV

Full-thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures (e.g., tendon or joint capsule) occurs in stage IV.

Location

The location of the pressure ulcer identifies the position in which the patient remained for too long. Pressure ulcers occur over bony prominences, and the most common sites for pressure ulcers are coccyx/sacral, trochanter, and ischial areas, as well as the heels. However, elbows, ears, and occipital areas are also common pressure ulcer sites.

Size

The length, width, and depth of an ulcer must be measured, and checks should be done for sinus tracks, undermining, and tunneling. Measurements of these areas can be accomplished by using a sterile Q-tip or tongue blade.

Characteristics

It is important to note the presence of any granulation tissue, epithelialization, necrosis, and slough; measure the percentage present; and document these findings. If drainage is present, the amount, color, and consistency should be documented.

Periwound

The tissue surrounding the ulcer should be inspected, and any maceration, excoriation, or signs of infection, such as warmth or induration, should be noted.

Goals of Treatment

The goal of patient comfort may take precedence. A patient who experiences pain or agitation on turning or during administration of tube feedings may simply wish to forgo the sort of intensive management that may be required to heal advanced pressure ulcers (23).

Local Care

Goals are established for the care of the wound based on a thorough assessment of the ulcer and the patient. Setting goals for local ulcer care and consistently assessing for progress toward these goals allows new objectives to be set when goals have been met (22). If débridement is the goal, dressings that encourage débridement are no longer necessary once the necrotic tissue has been removed. Topical treatment of wounds involves the goals of cleansing, débridement, reduction of bacteria, and protection. Table 22-4 describes product selection based on the interventions derived from wound assessment.

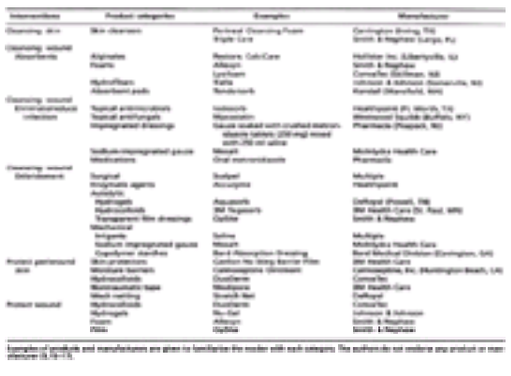

TABLE 22-4. WOUND CARE PRODUCT SELECTION FOR PRESSURE ULCERS

Cleansing

Skin. Cleaning the skin involves the removal of wastes and drainage from the skin around the wound. This goal can be accomplished easily by using skin cleansers that emulsify waste materials for ease of removal. Many of these also neutralize odors, which makes them excellent for use on the incontinent patient. Use of these skin cleansers facilitates the removal of surface debris without irritation to the epidermal layers. Some do not require rinsing, and others contain moisturizers that may interfere with adhesion of tapes or dressings. The manufacturer's directions should be followed for each specific product.

Wound. There are a few appropriate methods of cleansing a wound. Absorption of drainage and debris along with preservation of a moist environment or flushing with fluid to remove debris are appropriate methods of wound cleansing.

Absorbents. Absorbents absorb the exudate and debris from the wound and surrounding tissue. In this way, they reduce drainage and even edema from surrounding tissue while cleansing the wound and preserving a moist environment. They vary in the manner in which absorption occurs and the amount of drainage they can absorb. Many absorbents are used to fill in dead space and maintain a moist interface with each wound surface.

Irrigants. These fluids are used as mechanical cleansers to clean surface debris. It is the force of the fluid that accomplishes the results rather than the composition of the fluid itself; therefore, irrigants should be chosen with care. Sometimes, irrigation fluids are used to wet dressings for packing into wounds to eliminate dead space. Some of these fluids have been found to have some cytotoxic activity and thus may interfere with or delay wound healing (21). Irrigants that have been shown to be nontoxic are preferable, especially for the clean, noninfected wound.

Débridement. There are three main methods of débridement: autolytic, whereby the body's own fluid breaks down necrotic tissue; chemical, whereby chemicals

containing enzymes erode the necrotic tissue; and mechanical, which involves a mechanical force to disrupt the necrotic tissue.

Autolytic Débridement. Autolytic débridement is also known as *self-débridement* and includes the following:

1. Occlusive (moisture retentive) dressings: trap exudate, enabling white blood cells to liquefy and phagocytize necrotic tissue. This is selective (specific) débridement in that only necrotic tissue is affected.
2. Film or moisture vapor-permeable dressings: semiocclusive dressings in that they allow the exchange of gases and vapors but trap exudate under the dressing.
3. Hydrogels/gels: aid in rehydration of necrotic tissue, enabling autolysis to occur. These must be kept moist and not allowed to dry out.

Chemical Débridement. Enzymes chemically digest debris and necrotic tissue. Eschar must be cross hatched to facilitate penetration of enzymes. Surrounding skin must be protected from moisture. Iodine renders some chemical débriders ineffective, as does a change in the pH of the wound. Some require a moist environment and multiple dressing changes. As with all dressings, the specific manufacturer's directions must be followed.

Mechanical Débridement

1. Impregnated gauze: creates a hypertonic environment, which causes wound fluid to soften necrotic tissue. It must be used on wet wounds because it is ineffective on dry wounds.
2. Surgical débridement: most effective in selective dissection of necrotic tissue.
3. Wet to dry dressings: plain gauze, as it dries, traps debris that is removed when dressing is removed. It is nonselective in that all tissue, both necrotic and viable, is removed with the dressing. Gauze with large interstices to trap debris should be used.
4. Whirlpool/irrigation: the removal of necrosis and debris with fluid as the mechanical force.

Protection

Skin

1. Creams and lotions: lubricate and soften skin to promote rehydration.
2. Ointments: form an occlusive barrier over skin to protect from chemical irritation as in the presence of wound drainage or incontinence.
3. Skin sealants: form a layer of plastic polymer over the skin to protect it from friction of tape removal and irritating drainage. Some contain alcohol and sting if applied to denuded skin. One new product contains no alcohol and can be applied to excoriated skin.
4. Gelatin/pectin or hydrocolloid wafers: form seals over the skin. These are excellent dressings to use under tapes.

Wound

1. Moisture vapor-permeable dressings: semiocclusive dressings that allow the exchange of gases and vapors; they are helpful for the protection of superficial wounds.
2. Gelatin/pectin wafers, hydrocolloid wafers (occlusive-moisture retentive dressings): seal off a wound to protect it from the outside world. No fluid or bacteria can penetrate the hydrocolloid dressings. In addition, they provide the wound with an optimal healing environment. Because fluid is formed over the wound bed, trauma from dressing removal is eliminated. These are quite useful with incontinent patients.
3. Ointments and gels: provide a protective, moist environment for wounds and prevent desiccation.

Many of these treatments must be reapplied often to maintain a moist environment. Always refer to the package inserts and follow the manufacturer's directions to achieve optimal outcomes.

SUMMARY

People who are receiving palliative care are at great risk for acquiring pressure ulcers and at further risk of poor wound healing once ulcers do occur. However, a few small studies (4,5) have shown that those principles of care applied in acute care may also be useful within palliative care. Indications that pressure sores may be prevented in some instances and that healing can take place in the weeks leading up to death are beginning to be observed. Although these are not clinical research studies, they do reflect a willingness to identify interventions to deal with pressure ulcers and thereby improve quality of life in this patient population (Table 22-4).

MANAGEMENT OF MALIGNANT CUTANEOUS WOUNDS

The research-based evidence in the literature to guide caregivers in the management of malignant cutaneous wounds is sparse (26,27). Since 1966, approximately 90 articles have been published in recognized journals. Although the prevalence *is* low, these wounds present significant challenges for the patient and their health care providers (28,29) because they progress from skin erythema to a fungating mass with infection, bleeding, and odor. The information currently available in the literature concurs that management and assessment should be based on a holistic and interdisciplinary approach (30).

Definition

Malignant cutaneous wounds infiltrate and proliferate into and through the epidermis of the skin and are also referred to as *fungating* or *ulcerated wounds*. The patient may present with a cutaneous wound from a rapidly growing tumor, end stage disease, or from a tumor that was untreated or ignored (29,30,31 and 32). They occur in 5–10% of persons with metastatic disease and skin involvement, most often during the last 6 months of life (29). The wound originates from a local tumor, such as a basal cell or squamous cell carcinoma or a malignant melanoma. These wounds can also metastasize along a suture line after surgery for a primary lesion, from recurrence of a cancer, or via the lymphatics or bloodstream from a distal primary lesion. They grow rapidly, with either a fungus- or cauliflower-like appearance, or may ulcerate and form shallow craters. Some of these wounds are malodorous, exudative, and hemorrhagic, with sinus tracts or fistulas, and may cause pain and infection.

Pathophysiology

As the tumor infiltrates the skin, malignant cells spread through pathways of least resistance such as tissue planes, blood and lymph, capillaries, and perineural spaces. The tumor extends throughout the skin presenting as a fungating, foul-smelling mass. The smell is caused by the organisms *Proteus, Klebsiella, and Pseudomonas*. In addition, the blood, lymph interstitial tissue, and intracellular and extracellular compartments can be affected, resulting in disturbances in hemostasis. The tumor develops its own blood supply, which it may subsequently outgrow, resulting in necrosis in the center of the tumor. Abnormalities in the vascularization of the lesion and surrounding tissue result in hypoxic areas that provide a medium for anaerobic organisms to proliferate in the necrotic tissue. This results in the characteristic smell and exudate associated with these wounds. The hyperpermeability of the tumor to fibrinogen and plasma colloid, and the secretion of vascular permeability factor by many tumors, contributes to the large amount of exudate. Bleeding is caused by the neovasculature and pressure on adjacent tissues (28,30).

Malignant cutaneous wounds may occur as a solitary lesion or in a group. The color ranges from pink to red, violet, brown, or skin color. Many present as a sore that will not heal, progressing to a hard mass fixed to underlying tissue and then to a friable ulcerating lesion with purulent exudate, odor, bleeding, pain, and pruritus (27).

Etiology

Malignant cutaneous wounds are most often associated with cancer of the breast, lung, head, neck, oral cavity, stomach, kidney, bladder, uterus, cervix, vagina, vulva, ovary, colon, lymphoma, and skin. Collier (28) identifies the location of these wounds as follows: breast, 62%; head/face, 24%; groin/genitals, 3%; back, 3%; and others, 8%. The most prevalent types are breast cancer for females and lung cancer for males (27,30).

Goals of Management

Patient comfort is the primary aim of management, with a focus on control of symptoms such as pain, infection, bleeding, odor, exudates, and cosmesis. Toward that end, goals for the patient are to improve quality of life, maintain dignity, maintain independence, and foster self-esteem (29,30). The goals for management are to control tumor growth and bleeding and to preserve and restore tissue viability (28).

Assessment

The health care provider must perform a holistic assessment in consultation with the patient and caregivers. Assessment techniques must be appropriate and practical, based on the problems as perceived by the patient and family. There are several parameters to address for wound assessment.

Psychosocial Issues

The effects of the cutaneous malignant wound are devastating. The patient's previous coping skills, feelings, and reactions to the wound, as well as to the primary disease, should be assessed (33). There are several quality of life issues related to a malignant cutaneous tumor that may cause reactions such as fear, anxiety, depression, denial, anger, guilt, blame, loss of control, and lowered self-esteem. The patient may have difficulty with symptom management and feel embarrassed and isolated. The disease may be advanced and uncontrollable with accompanying pain management issues. The odor can cause a social stigma and inhibit intimacy. Self-image and sexuality can also be affected, with feelings of lowered self-worth regarding cosmetic appearance. The health care provider must be sensitive to the physical, psychological, spiritual, and emotional consequences of the disease (30).

Wound Characteristics

Wound appearance is described in terms of the percentage of viable or nonviable tissue. Terms used to describe the wound are *necrosis, slough, bleeding, ulceration, or granulation*.

Measurements of the size of the wound are vital to determine if the wound is improving or deteriorating. A paper ruler or camera with a scale within the frame can be used to obtain objective measurements for length, width, depth, and any undermining. Due to the friability of these wounds, it is not recommended to trace them on a clear paper covering, as bleeding may be induced (28).

Odor is assessed by the subjective report of the patient and family. Odor may indicate necrosis or infection. It can be foul or sweet.

The condition of the periwound skin should be assessed. Signs of local infection include inflammation, erythema, heat, or pain. The patient may also be febrile and have an elevated white blood count if the infection is systemic. The local area may be edematous or tender, and a fungal rash may be present.

Pain assessment involves noting the type of pain, severity, duration, precipitating factors, and impact on activities of daily living.

Exudate is assessed for color, consistency, and amount. Increased drainage may be indicative of infection; areas of maceration should be noted.

Wound characteristics should be assessed and documented on initial assessment and weekly thereafter. Accuracy and consistency of wound assessments can be facilitated through the use of charts (36), which can be used by the multidisciplinary team to evaluate the current status of the wound. Based on the wound assessment, planning can then begin to determine the treatment objectives. The treatment objective then drives decisions for treatment regimens.

Management/Interventions

Antineoplastic Treatments

Antineoplastic treatments include radiotherapy, surgery, cryosurgery, laser therapy, and cytotoxic or hormone replacement therapy (28,33). Palliative radiation can provide symptom control by decreasing pain, bleeding, and exudate. It may also preserve structure, function, and cosmesis. Chemotherapy or hormonal therapy can relieve tumor symptoms by reducing tumor size, pain, and bleeding. Surgical intervention can be used to excise or debulk the tumor or minimize the risk of fungation. Laser therapy reduces pain and necrotic tissue in preparation for possible excision of the tumor and skin grafting (29,34). All symptomatology exhibited by the patient must be addressed to achieve optimal patient outcomes.

Local Wound Care

Wound Care Product Selection

Caution must be used when selecting a dressing to ensure it will not interact with any course of treatment at the time, such as use of occlusive dressings during radiation treatments (28). Other considerations for wound care products include cost, number of dressing changes, availability, ease of application, and education (35). Dressing selection is predicated on the assessment process. Table 22-5 describes product selection according to interventions that are derived from wound assessment.

TABLE 22-5. WOUND CARE PRODUCT SELECTION—MALIGNANT WOUNDS

Wound Cleansing

Wound cleansers remove exudate and necrotic tissue from the wound bed, providing odor management, débridement, reduction of bacterial load, and cosmesis. Cleansing should be gentle to prevent pain, further trauma, or bleeding. Products that achieve this goal include irrigants (such as commercial cleansers and saline) that mechanically cleanse the wound, and absorbent dressings.

Pain

The amount of pain is dependent on the position of the wound site, degree of disease, nerve involvement, soft tissue damage, and the individual's pain tolerance.

To minimize the level of pain and trauma, maintain a moist wound environment and reduce the number of dressing changes. Examples of dressing categories that accomplish these goals include contact layer dressings, nonadherent gauzes, coated gauzes or impregnated gauzes, and semipermeable foam dressings. Anesthetic gels or systemic analgesics may be needed to reduce pain and can be administered before the dressing change (34).

Odor

Wound cleansing, containment of drainage, dressings with an airtight seal, and proper disposal of soiled dressings are the first steps for odor control. Wound cleansing helps to remove necrotic tissue and reduce bacterial growth. Débridement can also be instituted to remove necrotic tissue. There are several products that can be used for odor control. Topical metronidazole gel can be applied to the wound or given by a suppository (29). Charcoal dressings are available that are odor absorbent with antimicrobial activity. Sodium-impregnated gauze can also be used to control odor. External deodorizers and air fresheners that mask odors are rarely used, as they

can be nauseating when mixed with wound odor.

Exudate

Copious amounts of exudate can be absorbed with alginates, foams, and hydrofibers in conjunction with absorbent pads. Dressings should be changed once strikethrough (the drainage can be observed through the back of the dressing) is present. Large amounts of drainage can be contained with a drainage pouch if dressings require changing more than every 4 hours (40). Some of these pouches provide access to the wound without removal for dressing changes, and also have adaptors to connect to over the bedside drainage (such as a urinary collection bag) for highly exudative wounds.

Bleeding

Care must be taken when removing dressings to prevent bleeding. Warmed normal saline irrigation can be used to further moisten the dressing to prevent adherence to the wound. Capillary bleeding can be reduced with silver sulfadiazine (34). Alginates, collagens, and nonadherent gauzes provide hemostasis for light bleeding and absorption without adhering to the wound bed. Bleeding can also be stopped with local pressure for 10–15 minutes. For bleeding that continues, hemostatic dressings, such as gelfoam, can be used to promote clotting (29). In addition, cautery can be achieved with silver nitrate sticks. For profuse bleeding, ligation or cauterization may be necessary.

Infection

As the necrotic tissue becomes colonized with aerobic and anaerobic bacteria, infection can result. If the wound shows signs of clinical infection such as induration, inflammation, erythema, heat, or pain, a biopsy of viable tissue is necessary to determine systemic antibiotic therapy. Topical antimicrobial creams, gauze dressings soaked with crushed metronidazole tablets (250 mg) mixed with 250 ml normal saline, and sodium-impregnated gauze can reduce bacterial loads. For systemic infection evidenced by fever, leukocytosis, or cellulitis, oral antimicrobials or oral metronidiazole may be indicated. Fungal infections can be treated with topical antifungals.

Periwound Skin

Exudate can cause maceration of the periwound skin. This area can be protected with skin protectors or moisture barriers. A more absorbent dressing or more frequent dressing changes may be indicated. Prevention of periwound maceration also reduces pain. This is achieved through the use of protective barrier films, cream or ointment barriers, hydrocolloid barriers, nontraumatic tape, and mesh netting to anchor dressings.

Débridement

Débridement is achieved by surgical, enzymatic, autolytic, or mechanical methods.

Autolysis can be achieved with hydrocolloids, hydrogels, or transparent film dressings. Enzymatic agents chemically débride necrotic tissue. Mechanical methods include irrigants, sodium impregnated gauze, and absorbent products.

Cosmesis

Patient participation is important so as to choose a dressing that is aesthetically acceptable. The goal is to restore symmetry. Dressings that are low profile or fill a defect may be used to maintain symmetry. Other team members that can assist with cosmesis include social services, psychiatry, image consultants, or cosmetologists (34).

SUMMARY

The primary goal of management for malignant cutaneous wounds is the control of the symptoms. Realistically, the goals are to provide an optimal environment for wound healing; reduce odor, drainage, and pain; and provide psychosocial support.

A holistic assessment in consultation with the patient enables the health care provider to implement the optimal wound dressing and provide psychological, emotional, social, and spiritual comfort for the patient. Caregivers should be included in this process to assist the multidisciplinary team in meeting all the needs required for the patient with a malignant cutaneous wound.

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23

LYMPHEDEMA

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Lymphedema is an abnormal accumulation of tissue proteins, edema, and chronic inflammation caused by damaged or blocked lymphatic vessels. Significant discomfort, impaired function, and unsatisfactory body image resulting from this complication to cancer and its treatment can cause individuals profound morbidity and adversely affect their quality of life.

Although lymphedema can be congenital *(primary*) or acquired *(secondary*), only lymphedema secondary to malignant disease is discussed in this text. Acquired lymphedema secondary to cancer is often considered benign and not life-threatening. Accordingly, lymphedema remains poorly researched and understood, and its true occurrence is probably underdiagnosed. No clearly defined, universally accepted diagnostic guidelines have been developed or used, and as a consequence, treatment is often ignored. All too often, comments such as “You will have to live with it” or “There is nothing we can do to help” are the conclusions presented to patients. In other cases, well-intentioned but inappropriate treatment may be initiated.

Based on the studies available to date, it is clear that the incidence and prevalence of lymphedema secondary to all types of malignancies make it a common condition, one that instills significant morbidity in patients as well as having far-reaching implications in our health care systems.

PATHOPHYSIOLOGY

The lymph vascular system's function is to clear the interstitial spaces of macromolecules (proteins too large to reenter the blood vessels directly) and the water that acts as their carrier from the tissues and transport them back to the intravascular circulation (1) (Fig. 23-1). Normally, this process relies almost entirely on local tissue movement to induce the lymph flow. The flow is therefore a passive process that is dependent on changes in local hydrostatic and osmotic pressures.

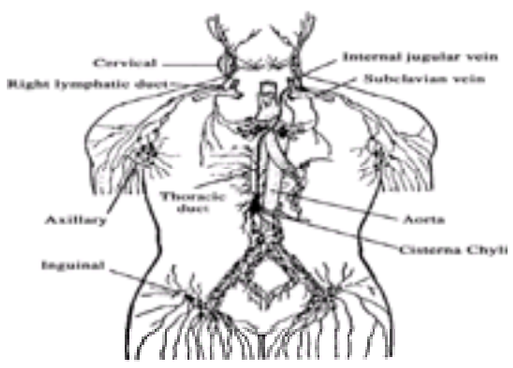

FIGURE 23-1. The lymphatic system.

Although pure lymphedema remains poorly understood and clinically difficult to induce, it is generally accepted that it occurs when lymphatic production exceeds the lymphatic transport capacity. In most patients with lymphedema secondary to malignant disease or due to treatment of the disease, an obstruction of lymph drainage occurs, resulting in a gradual buildup of the macromolecule proteins within the tissues. The resultant failure of the lymph vascular system to maintain an adequate drainage capability, in combination with an inadequate scavenging of stagnating plasma proteins by macrophages, results in progressive chronic lymphedema.

Chronic edema rarely, however, arises from the failure of one system alone (2). Damage to the vascular system as a result of surgery, radiotherapy, or progression of the disease also frequently causes damage to other vessels. Edema is therefore often secondary to blocked lymphatics plus venous stasis. Recent studies suggested that the pathophysiology of edema in postmastectomy patients may involve several additional mechanisms, including a possible rise in capillary blood pressure, which in turn may cause an increase in net capillary filtration, placing an increased load on already damaged lymphatics (3).

PATIENTS AT RISK

Factors that contribute to the development of lymphedema include radical surgeries and extent of lymph node dissection, radiation of lymph nodes, postoperative wound complications, and subsequent cellulitis of the limb.

Patients most at risk of developing secondary lymphedema are as follows (4):

1. Breast cancer patients who have had surgery involving nodal dissection. There is an added risk if such patients have undergone postoperative radiotherapy.
2. Patients with malignant melanoma of the arms or legs with nodal dissection or radiotherapy.
3. Prostate cancer patients who have had surgery or whole pelvic radiation.
4. Patients with gynecological cancers with advanced disease, surgical procedures, or radiotherapy.
5. Patients with advanced testicular cancer.
6. Patients suffering advanced neoplastic disease in which the metastatic spread is found in the lower quadrants of the abdomen, thus impeding venous and lymphatic drainage.

Other factors, such as advanced age, poor nutritional status, and obesity, should be monitored as they may lead to delayed wound healing, which in turn is an important risk factor for the development of lymphedema. Other concomitant diseases, such as diabetes, renal failure, and cardiac disease, also aggravate edema of a limb (5).

INCIDENCE

The overall incidence of lymphedema is difficult to determine. Research published on its incidence and prevalence tends to be variable, and can also be misleading because the diagnostic criteria has not yet been standardized, the type and extent of surgery are variable, and the length of the studies undertaken is frequently too short to include patients with lateonset lymphedema.

For most patients, no investigations are currently routinely performed to determine whether the edema is entirely secondary to lymphatic obstruction or also involves damage to other vascular structures. In addition, statistics reported in specific studies tend to refer to lymphedema from one particular malignancy alone, the most widely studied and reported being breast cancer.

Breast cancer is currently the most prevalent malignancy in women in the United States. It is projected that it will affect one in nine women during their lifetime. Surgical and medical therapies based on mastectomy and radiotherapy are increasingly extending patient life spans, but these procedures also may place patients at high risk of developing lymphedema (6). Primarily because of the nonstandard reporting criteria outlined earlier, the available literature suggests that the overall incidence of lymphedema in patients with breast cancer who have had surgical intervention, with or without radiotherapy, is between 6.7% and 62.5% (7,8 and 9). The research, however, does agree that axillary node clearance and postoperative radiotherapy do increase the risk for developing lymphedema, with radiotherapy cited as the most important risk factor (10,11).

Although the reasons for performing either axillary or groin nodal dissections during surgery may have changed from being solely therapeutic to also being important for staging and diagnostic potential, it still causes profound disability by increasing the risk of lymphedema (12). Early detection and longer survival also have increased the incidence and length of time patients experience this complication.

TYPES, STAGES, AND GRADES OF LYMPHEDEMA

Edema is generally not detectable clinically until interstitial volume reaches 30% above normal. Symptoms have been reported to occur immediately after surgery and to persist. In most cases, however, lymphedema first occurs 18–24 months after treatment. It has been reported to occur as a new finding even 30 years after diagnosis and treatment of malignant disease.

There are four specific types of lymphedema (13):

1. Acute transient and mild occurring within a few days after surgery as a result of cutting lymphatic channels. It usually responds to elevation and exercise such as muscle pumping (i.e., making a fist and releasing it).
2. Acute and painful edema occurring 4–6 weeks postoperatively as a result of acute lymphangitis or phlebitis. This can be successfully treated with elevation and antiinflammatories.
3. The third type is an acute erysipeloid form, which often occurs after an insect bite or other minor injury or burn and can be superimposed on a chronic edematous limb.
4. The most common form of lymphedema is insidious and painless and is not associated with erythema. It develops much later and is most apparent 1–2 years after treatment. It is the most difficult edema to reverse because of its pathophysiology. This chronic lymphedema occurs secondary to a deficient lymphatic system that is incapable of compensating for the increased demand for fluid drainage. Consideration should always be given in this patient population to rule out recurrence of disease.

This last and most prevalent form of lymphedema is staged according to appearance of the limb and response to management. During the early stage edema is pitting and decreases with elevation of the limb. As the condition progresses untreated, the edema becomes firm and nonpitting, this change being secondary to chronic inflammation, fibrosis, and sclerosis caused by stagnation of the plasma proteins. The late stage results from the overproduction of connective tissue, resulting in hardening of the skin, and the condition is commonly referred to as *lymphostatic elephantiasi*s.

Lymphedema is often graded using the following scale (14):

1. Edema that is barely detectable.
2. A slight indentation is visible when the skin is depressed.
3. A deeper fingerprint returns to normal in 5–30 seconds.
4. Edema is the maximal grade; the affected extremity may be 1.5–2.0 times its normal size.

This scale has limitations, however, and can be used only during the early stages or when edema is pitting.

INVESTIGATIONS

Lymphography and lymphangiography previously were considered the “gold standards” for demonstrating lymphatic abnormalities. These techniques are, however, invasive and difficult to perform in the presence of edema. They also are limited in providing information on anatomical detail and frequently visualize only the large subcutaneous collecting lymphatics (15).

Quantitative lymphoscintigraphy (isotope lymphography) (16,17) has been more useful in detecting lymphatic insufficiency because the dynamics of flow and rate of transit via lymphatic vessels are studied using a gamma camera. It is also a more comfortable procedure for the patient because it is administered by an interstitial injection instead of direct cannulation of peripheral lymphatics.

Magnetic resonance imaging is also sometimes used to view soft tissues and lymphatics and is even less invasive. Color Doppler (18) has been used to define or rule out venous abnormalities and can be useful in patients for whom more invasive tests are contraindicated or inappropriate.

In general, for determining the management of lymphedema symptoms, invasive investigations are frequently not necessary in patients with acquired lymphedema secondary to cancer. They may, however, be helpful in determining the management required for patients who do not respond to conservative treatment or in whom a mixed etiology of limb edema is suspected.

CLINICAL ASSESSMENT

A full clinical assessment for lymphedema (Table 23-1) should address the history of the primary disease, including previous surgery, any nodal dissection, and radiotherapy. It also should include a full history of the duration of the edema, symptoms, complications, and past treatments. The physical examination must include measurements of the affected limb and the contralateral normal limb for comparison. An assessment of motor and sensory function is imperative, and pulses should be checked. It is also helpful to be aware of the cardiac and renal function of each patient, as treatment to mobilize fluid could put added strain on these organs.

History
Primary disease (including surgery, nodal dissection, and radiotherapy)
Lymphedema (duration, symptoms, complications, treatment)
Functional and social history
Changes in activities of daily living, depression, self-esteem
Physical examination
Inspection
Pulses
Motor function
Sensory function
Measurement of affected and normal limbs

TABLE 23-1. CLINICAL ASSESSMENT

Although pain and other discomforts are common complaints, patients are often even more concerned about the “heaviness” and loss of function in the limb. Many describe the limb as “ugly” and find it impossible to wear their own clothing because of the physical size of the affected limb.

A functional history with specific questions concerning activities of daily living, difficulty with clothing, and other possible limitations secondary to the edema are essential. The patient's sense of self or selfesteem and any possible signs and symptoms of depression need to be assessed. Patients frequently feel they have lost their independence and freedom because of both the difficulty experienced in managing the activities of daily living with the often “useless, heavy arm or leg” and the embarrassment of going out and meeting people with “this deformity.” For all these reasons, the patient's quality of life is often severely compromised and should be considered to constitute an integral part of the treatment process.

MONITORING

The size of the limb should be measured before treatment is begun and then at regular intervals during management to permit detailed monitoring of the patient's progress. Several methods of measurement have been used in the past (19). In some centers, the arms are measured at only one location and compared with previous measurements, with a difference of 2.5 cm indicating moderate lymphedema. Other centers use the same basic method but take measurements at two or three levels and compare the results. These methods tend to be unreliable because of the variability of the shape of the limb from point to point and because of differences in shape before and after treatment. Other practitioners advocate submersion of the limb in water and measuring the volume of the displaced liquid. This method, although considered the most accurate, is a complicated and often messy procedure that makes it impractical for home use.

An accurate and more practical method of assessing volume of the limb is shown in Figure 23-2, which demonstrates measurements for the upper limb. The circumference of the arm is taken at 2-cm intervals using a tape measure with weights at either end, which are allowed to hang freely. Assessment bias can occur if the examiner adjusts the tension on the tape. An adapted formula for the volume of a cylinder is used to determine the volume of the arm from wrist to axilla. This methodology is more precise than using only a few comparative points and allows more accurate and detailed comparisons with the other arm and with the same arm over time. It is also much easier and less cumbersome than submersion in water and can be undertaken readily in the patient's home. It does not, however, provide for the volume of the hand, which must be determined and compared separately.

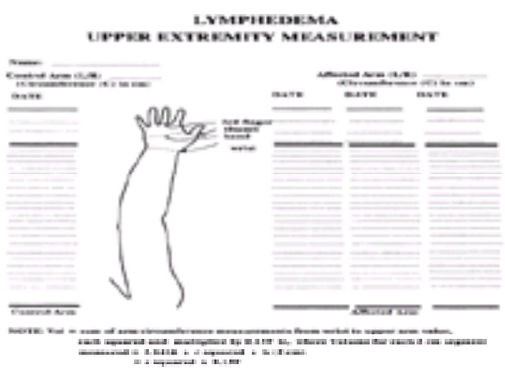

FIGURE 23-2. Technique for measurement of upper extremity lymphedema.

Perhaps more important than the particular method used is the need for consistency in the technique used (Table 23-2) (20). A decrease in limb size indicates that treatment is beneficial and should be maintained. More importantly, such a result also tends to encourage patient compliance because a measurable improvement can be seen readily; this is particularly important at times when visual changes are not obvious. Volumetric measurements provide a quantitative result and are extremely valuable for determining and following the treatment progress.

At each measuring occasion:
Position the limb at the same height
Remark the limb
Record the starting point accurately
Ensure that tension is not applied to the tape measure
Ensure that the tape measure is straight
Use the same number of measurement

TABLE 23-2. GUIDELINES FOR LIMB VOLUME MEASUREMENTS

Several other methods of assessing and monitoring lymphedema are currently being investigated. Studies to assess the elasticity and the viscosity of skin by using a technique involving vertical extensibility by suction may prove useful in assessing functional difficulties in relation to skin infiltration and may be useful in followup (21). Subcutaneous interstitial fluid pressure and arm volume also can be measured by the wick-in-needle method (22). Multifrequency bioelectrical impedance analysis may offer a means to an earlier diagnosis and more accurate monitoring of extracellular fluid changes during and after treatment (23). It is unclear at this time whether any of these techniques offer any information beyond that provided by a good clinical assessment.

PREVENTION

The ultimate prevention would be a change in the method of diagnosing and treating the previously mentioned malignancies. A change from aggressive, disfiguring surgeries such as radical mastectomies to more conservative lumpectomies for breast cancer has been helpful in decreasing many postoperative complications, including lymphedema. As removal of lymph nodes during initial surgery has also increased the incidence of lymphedema, any reliable method to eliminate this procedure while obtaining the same results would also be very important in preventing this unpleasant complication. The lymph nodes are small structures (approximately the size of a small pea) located throughout the body that serve as an immunological filter. In patients with a breast malignancy, cancer cells migrate to the lymph nodes in the axilla. During axillary node dissection, a sample of five to ten of the existing (over 50) small nodes are removed to be studied microscopically. A sentinel node biopsy is a new procedure presently being investigated in an attempt to reduce the extent of axillary node dissection by removing the one node most likely to have cancer cells (24). This technique uses a combination of a radioactive tracer and a color dye. The dye is injected around the tumor or into the biopsy cavity. The dye migrates through the lymphatic channels to the regional lymph nodes drained by the cancer. The specific node most likely to be involved with cancer is then identified and only this node is removed for analysis. This method can be nearly as effective as an axillary dissection. Although the research is not completely refined, the goal is to find a noninvasive test that is even more predictive than axillary dissection.

Ideally patients should be assessed preoperatively and taught the appropriate exercises to squeeze soft tissue and encourage proximal lymph flow. These exercises then would be continued postoperatively (25). The main problem with this prophylactic treatment plan is compliance. Not surprisingly, patients who have never experienced the symptom of lymphedema personally have a tendency to feel complacent and believe that this will never happen to them; therefore they stop treatment.

Patients also should learn to recognize early warning signs, such as tightness, aching, pain, or other sensory changes in the limb. Any signs of infection or cellulitis should be reported and managed appropriately, and delayed wound healing should be regarded as a risk factor for the development of lymphedema.

TREATMENT

Although the full pathophysiology of lymphedema is poorly understood, the edema experienced in a limb, whether secondary to the primary diagnosis or resulting from treatment for the disease (e.g., surgery and radiotherapy), is probably multifactorial, with damage not only to lymphatics but also to the venous circulation system and other tissues as well. For this reason, treatment also must be variable. However, lymphedema is a chronic condition, and therefore treatment must also be chronic. To be effective and to encourage patient compliance, treatment must be consistent, clearly understood, and convenient.

Management of lymphedema is extremely variable in the medical profession, ranging from aggressive diagnostic procedures to precipitous operations. Scattered between these two extremes are quite a number of various conservative methods (5). Although treatment for lymphedema is usually the same for patients with or without active malignant disease, it is generally perceived that this treatment is more effective if there is no active disease present.

As early as 1855, in the German literature, surgeons Esmarch and Kulenkampff (26) described a treatment modality consisting of hygienic measures, elevation, and compression. Later, in 1892, Winiwarter (27), also a surgeon, advocated a similar conservative approach as the first choice of treatment. Excellent results were reported at that time; with minor alterations, this same treatment plan can still be very effective today. However, it must be remembered at all times that the single most important factor in management of lymphedema is patient compliance (28).

Treatment is most effective when a multidisciplinary approach involving physicians, nurses, massage therapists, physiotherapists, and occupational therapists is followed. As patient cooperation and compliance is of such great importance in the success or failure of what is often a lengthy course of treatment, an assessment by and continued consultation with a psychiatrist or psychologist is often also valuable in identifying problems and providing appropriate intervention related to the patient's overall psychological adjustment (29). Treatment consists of several basic but important elements (Table 23-3), which should be used in combination for maximum results (30,31).

Education
Manual lymphatic drainage
Massage
Compression garments
Bandaging
Compression sleeves or stockings
Exercise
Skin care
Consistent follow-up and compliance

TABLE 23-3. BASIC TREATMENT FOR LYMPHEDEMA

Education

Patients must be aware from the beginning that treatment probably will be required for the rest of their lives. It is important for patients to begin management as early as possible and to be consistent and dedicated. To enlist their active cooperation and compliance, they also need to be told about the predicted good results anticipated with treatment. Education includes a thorough discussion about the “do's” and “do not's” of caring for the lymphedematous limb (6). There are a number of things that can be done to manage lymphedema and avoid complications:

- Observe skin carefully each day and report any skin breakdown, weeping, or reddened areas to their doctor immediately.
- Avoid heavy lifting with the affected limb.
- Avoid use of hot tubs and saunas.
- Avoid cuts or burns to the affected limb by wearing gloves when gardening or doing housework.
- Refuse to allow blood pressure measurements or venipunctures from the affected limb.
- Maintain a healthy body weight.
- Exercise the limb regularly.
- Wear a compression sleeve when doing strenuous exercise or work or when traveling by air.
- Carry out self-massage daily, concentrating on using light pressure (if the skin turns red, the pressure is too firm). Ensure that strokes go up the arm to move the fluid out of the limb. Do not push fluid into the axilla. Spend more time on firm areas.

Manual Lymphatic Drainage

Recommended treatment for lymphedema is massage therapy plus the application of compression garments. This specialized treatment has several different names: *combined decongestive therapy, complex physical therapy, combined decongestive physiotherapy, and manual lymphatic drainage* (MLD). Regardless of the terminology, the treatment involves light massage, compression garments, exercise, and skin care. It is imperative that patients with lymphedema see their physicians before beginning treatment and that recurrence of disease, deep venous thrombosis, and cellulitis are ruled out (32).

A thorough knowledge of the mechanism and process of clearing the body of lymphatic waste must be understood before the treatment of MLD can be fully comprehended. The lymphatic system functions as a drainage and transport vehicle moving waste material from the interstitium. It removes proteins, fat, water, chemicals, organic and inorganic cellular products, and foreign organisms such as bacteria and viruses, clearing them from the interstitial spaces. This system relies almost exclusively on local tissue movement for lymph flow. The lymphatic vessels bring the fluid from the periphery to the lymph nodes, where it is filtered and the waste excreted and the useful material dumped back into the blood stream. The body has areas that have a high concentration of these nodes, known as *watersheds*. They are located in the neck, axilla, groin, and throughout the abdomen. These watersheds collect lymph from the body in quadrants. Although the nodes on one side of the body collect fluid from the same side quadrant (e.g., fluid from the lymphatic vessels from the right arm and right side of the trunk anteriorly and posteriorly superior to the umbilicus drain into the right axilla), there is some crossover between the right and left sides of the body. This communication is known as *lympholymphatic anastomoses* (33). Massage often takes advantage of this crossover to divert fluid to the contralateral fully functional lymph nodes. The lymphatic system can be further divided into superficial vessels situated just below the skin and superficial to muscle and deep vessels located near major veins and muscles. The fluid thereby is moved along superficial vessels by contraction of small muscles (and in the case of lymphedema, by the assistance of MLD or massage) and to deeper vessels and nodes by larger muscle contraction and venous flow.

MLD is a gentle massage technique that was developed in Europe in the 1930s. This very light massage directly affects the superficial lymphatics and helps to move the fluid along the pathways. The massage begins at the trunk and moves out to the periphery and back again. The massage starts at the neck, which is known as the *terminus*. This is where the lymph fluid returns to the bloodstream. The treatment begins here to clear the pathway so that it can accept more fluid. Then massage is continued on the unaffected side, with work on the chest and axilla for patients with upper extremity edema and on the abdomen and axillary nodes for those with lower extremity lymphedema. Again, this is to make room for the fluid from the contralateral side. Next we work on the affected side, directing all strokes to the unaffected side's axilla or to the abdomen. This is done to develop collateral lymphatics so they can handle the lymph-obligatory load (34). The limb is massaged gradually, moving distally until the hand or foot is reached. The therapist always follows the direction of the lymph flow towards the trunk. Once the hand or foot is completed the limb is massaged again, moving proximally to the trunk and collateral lymphatics. Treatment should last approximately 45 minutes per limb but can be considerably longer. For best results, treatment should be given twice each day for 2–4 weeks. These guidelines depend on the severity of the condition and patient availability. All during this process, more time is spent massaging any areas that are congested or firm due to buildup of fluid. Measurements should be taken every fifth treatment to monitor effects and encourage patient compliance. Once there has been a significant reduction in limb size, the compression bandaging can be replaced by a compression garment and the frequency of the treatment can be reduced (33).

Compression Garments

After massage treatment is completed, it is important to put some compression on the limb. This is done to preserve the positive results of the massage treatment. When the affected limb is under compression it increases the tissue pressure, resulting in a reduction of abnormal increased ultrafiltration and improved reabsorption. Compression also reduces fibrosis and sclerosis and increases the effectiveness of the joint-muscle pump (35). Ideally, the limb would be wrapped in a layer of foam

and short stretch bandages (Fig. 23-3, Fig. 23-4). A compression sleeve is often used instead for convenience, comfort, and ease of application. This is also something the patient can manage independently. The advantage of the bandages is that they create a higher pressure and usually obtain better results. For patients with very severe lymphedema, a prebandage combined with exercise can be done before treatment to get the fluid moving more quickly (33).

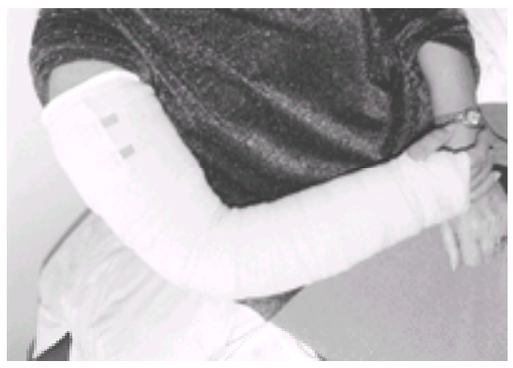

FIGURE 23-3. Patient with bandaging of upper extremity.

FIGURE 23-4. Patient with bandaging of lower extremity.

There are four standardized grades of compression. Grade I and II have little place in this treatment and are used more for superficial effects only in treating venous insufficiency. Grade III is used for superficial and deep tissue effects for grade I lymphedema. Grade IV is needed to produce a deep tissue effect for grade II and III lymphedema. Compression bandages are usually used for the initial treatment stage to quickly reduce limb size and compression garments to maintain this result long term (35).

Exercise

The third component to treatment is exercise; this is where patient compliance is especially critical. The joint-muscle pump assists in the movement of lymph and is, therefore, the key element in treatment. The exercises are not strenuous but rather simple range-of-motion-type exercises to keep muscles alternately contracting and relaxing to encourage lymph flow. There is no special equipment required. Exercises should be prescribed that fit within the person's pain-free range of motion and should only be done wearing a compression garment. The exercises should start distally and work proximally. It is important not to exercise too long or too strenuously, which could cause an unwanted increase in blood flow into the limb, possibly leading to more edema. It is recommended that each individual develop an exercise program that is comfortable for his or her general health, and increase the amount of exercise gradually as tolerated. The limb should also be elevated whenever possible to allow gravity to work on excess fluid (33).

Skin Care

The final but vital component to this treatment modality is good skin care. This is done to avoid any abrasions or irritations to the skin that could lead to infection. It is recommended that a water-soluble, fragrance-free lotion be used to moisturize the skin to avoid irritation (36). Abrasive products should not come in contact with the skin on the lymphedematous limb. The patient should also visually inspect the limb daily for trauma as sensory changes may have occurred, resulting in decreased perception to painful stimuli. If any abrasion or tear in the skin is found it should be treated immediately with an antibiotic cream (32).

It is imperative that MLD, which is the complete treatment of massage, compression, exercise, and skin care, be taught and performed by a qualified massage therapist or other health care professional with expertise and experience in this treatment modality. In time, patients (and families) can be taught to continue this treatment at home (37).

Intermittent Sequential Pneumatic Compression Pumps

Intermittent sequential pneumatic compression pumps have been used extensively in recent years to treat lymphedema, and some reported results have been encouraging, especially over the short term (38). However, for prolonged effects, patients in the studies still wore compression sleeves between sessions with the pump, and it is unclear whether the combination of pump and sleeve or stocking is any better over the long term than the compression garment alone. A study to evaluate the effects of pneumatic massage with uniform pressure, pneumatic massage with differentiated pressure, and manual lymphatic massage showed no difference between uniform-pressure pneumatic massage and manual massage, and both were better than differentiated pneumatic massage. Again, all patients wore compression garments between treatments (39).

Pneumatic pumps necessitate prolonged periods in clinic for treatment. Treatment becomes less accessible, more time consuming, and less convenient, all of which affects longterm patient compliance. Pumps may have a more beneficial effect in the early treatment of severe edema to soften the limb. A note of caution regarding in-home use of pumps is necessary. The use of sequential gradient compression pumps at home without the simultaneous MLD to prepare the healthy and impaired quadrants to receive the stagnant lymph being milked out of the edematous limb is a potentially dangerous medical practice. It often only relocates the site of the edema. In addition, excessive pressure can collapse the superficial lymphatics in a compromised system. Prolonged use of the pumps can also cause additional fibrosis and further exacerbate the lymphedema. Finally, these pumps are very expensive. For all these reasons, use of compression pumps has declined dramatically over the past few years.

If the pump is used, a compression garment must be applied afterward to prevent recurrence of edema, and care must be taken to ensure that the garment is not too tight if edema recurs. Pumps should never be used in patients with edema involving the trunk.

Other Treatment Modalities

A variety of other treatments deserve mention, as outlined in the following sections.

Antibiotics

Antibiotics should be used early, at any sign of cellulitis. Usually, oral penicillin or erythromycin is sufficient. When weeping edema is present, or for patients experiencing recurrent attacks of cellulitis, antibiotics may be required for a prolonged period (2).

Steroids

Steroids are often useful when edema is assessed to be secondary to obstruction by tumor or enlarged lymph nodes (2). If there are no contraindications to the use of steroids, a trial of dexamethasone is recommended in these cases only. This is best combined with MLD.

Diuretics

Diuretics act primarily by limiting capillary filtration and reducing circulating blood volume. They may be of benefit therefore in treating limb edema if the swelling is of a mixed origin; however, the function of the lymphatics is to remove protein and other macromolecules from the tissues. With the use of diuretics, fluid can be absorbed back into the vascular compartment, but proteins can return only via lymphatics, or can be broken down by phagocytosis. Diuretics therefore offer little improvement in true lymphedema and, in fact, may cause complications by mobilizing fluid from everywhere except the lymphedematous limb, resulting in hypotension and electrolyte disturbances (2). It is occasionally beneficial to combine steroids, diuretics, and MLD in patients with obstruction of the lymphatic system in the areas of the major lymph nodes due to active disease. The steroids are used to decrease inflammation at the site and open up the flow, the MLD to mobilize fluid, and the diuretics to promote renal excretion of excess fluid.

Benzopyrones

Coumarin, a 5,6-benzo(alpha) pyrone, has been used in Australia to treat lymphedema (40). It is available only in a few centers in North America. It reportedly has provided a therapeutic effect by stimulating macrophages to scavenge plasma proteins. The reduction in lymphedema is reportedly much slower than with decongestive therapy. It would seem reasonable that if coumarin is used, it should be in conjunction with physiotherapy to ensure treatment of both aspects of lymphedema: the decreased lymph flow and the abundance of proteins in the fluid.

Benzopyrones also may cause increased protein catabolism as a result of the continuous degradation of protein molecules. It is unclear at this time whether this could result in troublesome side effects in patients with an inadequate protein intake in their diets.

Diet

Diet, as a factor in the treatment of lymphedema, has not been widely studied. Two patients with idiopathic unilateral limb lymphedema responded to a diet with restriction of long-chain triglycerides (41). More research is needed to assess any possible benefit of this treatment on patients with lymphedema secondary to malignant disease. Obesity is, however, a factor that increases the risk of developing lymphedema.

Surgery

Surgical treatment of chronic limb lymphedema is either *physiologic* (an attempt to improve lymphatic drainage) or *excisional* (removal of edematous subcutaneous tissue with or without overlying skin) (42,43). This intervention is seldom appropriate in patients with malignant disease. Surprisingly, amputation is still occasionally advised for some patients with severe chronic lymphedema.

Intraarterial Infusion of Autologous Lymphocytes

This still experimental treatment was used in a few patients with refractory primary or acquired lymphedema with promising results, including a reduction in size, a decrease in pain, and softening of the limb (44,45).

COMPLICATIONS

Once treatment for lymphedema is initiated, compliance is of major importance. Factors that can negatively affect compliance include the amount of delay before starting treatment, the size of the limb when treatment is started, the availability of social and financial supports, and the presence of complicating health problems (46).

Untreated lymphedema leads to worsening of the symptoms of fullness, numbness, paresthesia, weakness, and pain. All too often the weight of the heavy arm in patients with upper-extremity edema can cause shoulder dislocation and further pain and loss of function. Lymphedema also plays an active role in the development of brachial plexus entrapment and carpal tunnel syndrome in patients who have previously had a mastectomy and radiotherapy (47). Recurrent cellulitis or erysipelas also occur more frequently in a lymphedematous limb and can, in turn, lead to further worsening of the edema (48). A more serious but rarer complication is lymphangiosarcoma, which is associated with lymphedema in patients with a previous diagnosis of breast cancer and subsequent radiotherapy treatment. The prognosis for these patients is poor, with metastases to lung, pleura, and chest wall occurring early in the course of the disease.

CONCLUSIONS

Lymphedema is not only a prevalent symptom in patients with cancer, but one that causes considerable morbidity and greatly affects patients' quality of life. It can occur secondary to the disease and subsequent treatment, especially surgery that includes nodal dissection and radiotherapy. Unfortunately, it can appear initially even years after the primary disease diagnosis and also can affect those in whom a cure or remission is achieved.

The treatment of acquired *(secondary*) lymphedema must be chronic and consist of several modalities. It must also, however, be relatively easy, convenient, inexpensive, and visibly effective to encourage patient compliance over the long term.

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24

PRINCIPLES OF FISTULA AND STOMA MANAGEMENT

DOROTHY B. DOUGHTY

A significant number of patients with solid tumors involving the abdominal organs have surgically created stomas or spontaneously occurring fistulas. Palliative care for these patients must provide effective containment of the effluent and odor, protection of the adjacent skin, and maintenance of fecal and urinary elimination. This chapter addresses the specific needs of patients with stomas or fistulas involving the intestinal or urinary tract.

FISTULA MANAGEMENT

Fistulas are abnormal openings between two internal organs or between an internal organ and the skin. The majority of fistulas arise from the gastrointestinal (GI) tract and are caused by delayed healing and anastomotic breakdown after a surgical procedure; fistulas may also occur as a result of direct tumor invasion or as a complication of radiation therapy (1,2,3 and 4). Fistula development is always a devastating development, and despite significant progress in management of complications such as sepsis and malnutrition, fistulas continue to be associated with significant morbidity and mortality. For the cancer patient, fistula development may be even more devastating; the addition of a fistula may overwhelm the patient's defenses, both physically and psychologically. Statistics indicate higher mortality rates among this patient population— for example, a retrospective review of patients treated at the National Institutes of Health Clinical Center from 1980 through 1994 revealed a 42% fistularelated mortality rate among cancer patients with enterocutaneous fistulas (2). In addition to the issues related to the fistula itself, the development of a fistula may delay or prevent treatment for the underlying malignancy, and malignant involvement of the fistulous tract may prevent closure, even with surgical intervention (2,4). Effective fistula management is thus a critical component of effective palliative care.

Classification Systems

Fistulas are commonly classified according to the organs involved, point of drainage, or volume of output (1,4). Fistulas are named according to the organs involved and the pathway followed by the effluent (Table 24-1). Fistulas also may be classified as internal or external. Internal fistulas involve an abnormal communication between two internal organs (e.g., enteroenteric or enterocolic fistulas). These fistulas may be silent in that they produce no obvious pathology, but they can greatly affect the patient's nutritional status by bypassing absorptive segments of small bowel (4). External fistulas are those communicating with the skin or with organs that drain onto the skin, such as the vagina. These fistulas produce obvious symptoms and present major challenges in management (4). The third mechanism for classifying fistulas is by volume of output. Fistulas producing more than 500 ml of output per day have been labeled *high-output fistulas*, and those producing 200–500 ml/day are generally classified as *low-* or *moderate-output fistulas* (1,4). As might be expected, high-output fistulas have a higher incidence of sepsis, malnutrition, and death than fistulas with low or moderate output (2).

Origin	Termination	Name
Small bowel	Skin	Enterocutaneous
Colon	Skin	Colocutaneous
Bladder	Skin	Vesicocutaneous
Small bowel	Vagina	Enterovaginal
Colon	Vagina	Colovaginal
Bladder	Vagina	Vesicovaginal
Rectum	Vagina	Rectovaginal

TABLE 24-1. TERMINOLOGY FOR COMMON FISTULAS

Phases of Fistula Management

Effective fistula management can be divided into several distinct phases: stabilization, investigation, conservative therapy, and definitive management (1,4).

Stabilization

Initial goals in fistula management include normalization of fluid and electrolyte balance, establishment of nutritional support, and elimination of sepsis (1,4). Specific fluid and electrolyte needs depend on the type and volume of fistula output; for example, small bowel fistulas usually produce high volumes of effluent containing potassium, sodium, magnesium, phosphate, and zinc (1,4). The patient with a high-output fistula requires close monitoring of fluid electrolyte balance, with replacement titrated in response to type and volume of output and based on laboratory indices. Fluid and electrolyte anomalies remain a significant problem in the management of these patients, and effective management can significantly reduce morbidity (1,4,5).

Malnutrition is another major problem associated with GI fistulas, especially high-output fistulas. Most of these patients require parenteral nutritional support, although continued low-volume enteral intake is frequently advocated to prevent atrophy of the villi (4). Aggressive nutritional repletion may sometimes be contraindicated for the patient with an underlying malignancy, especially if there is a delay in initiation of antineoplastic therapy. However, failure to provide nutritional support may result in a catabolic state that further compromises the patient's overall condition. Thus decisions regarding nutritional support for the cancer patient with a high-output fistula must be made within the context of the overall treatment plan and management goals (1,4). Fistula development is often associated with intraabdominal abscess formation, and sepsis is the most common complication of enterocutaneous fistulas. Therefore, initial management includes prompt management of any intraabdominal infectious process (i.e., drainage of all abscesses and initiation of appropriate antibiotic therapy) (1,4).

Investigation

The second goal in fistula management is to identify the origin of the fistulous tract and to elucidate any anatomical conditions that would prevent spontaneous closure of the fistula, such as distal obstruction, development of an epithelial-lined tract between the skin and the fistula opening (i.e., pseudostoma formation), complete disruption of bowel continuity, persistent abscess, or tumor involvement of the fistulous tract (1,4). Studies commonly involved in the investigative phase of fistula management include fistulograms (to identify the origin of the fistula) and computed tomography scans (to determine the presence of tumor involvement or persistent

abscess) (4).

Conservative Management

If there are no anatomical factors that would prevent spontaneous closure of the fistula tract, initial management is likely to be conservative in nature. This approach is based on studies indicating that a significant proportion of fistulas close spontaneously (if there is no inhibiting pathology), and on the fact that surgical closure is frequently ineffective until the underlying factors contributing to fistula development have been corrected (1,4). Even among cancer patients, spontaneous closure of fistula tracts is possible: Chamberlain reported a spontaneous closure rate of 33% for enterocutaneous fistulas (2).

Conservative management includes continued attention to fluid and electrolyte balance, nutritional repletion, and control of infection. In addition, measures are instituted to reduce the volume of effluent. The goal is to ensure sufficient intake of nutrients to support the healing process while minimizing the volume of drainage through the fistulous tract. Specific measures to reduce fistula output include limitation (or elimination) of oral intake and administration of octreotide acetate (1,4). Octreotide acetate is a synthetic somatostatin analog that is given subcutaneously to reduce the volume of intestinal secretions and to prolong GI transit time. The data on octreotide acetate's impact on fistula volume and fistula closure are inconclusive; however, in general, octreotide acetate has been shown to reduce the volume of fistula output, and in some studies has appeared to significantly reduce the time frame for spontaneous closure. To date, there is no evidence that octreotide acetate actually increases the number or percentage of fistulas closing spontaneously, so the clinician must weigh the potential benefit against the expense and discomfort of repeated injections (3,4,6,7). The decision to restrict oral intake must also be made within the context of the overall treatment plan, as such restrictions can significantly affect quality of life (5). If oral intake *is* significantly restricted, it may be beneficial to administer H_2 receptor antagonists to prevent stress ulceration and to reduce gastric secretions (4).

Definitive Therapy

When it is recognized that spontaneous closure is unlikely or impossible, a determination must be made regarding further management. The two options are palliative management (with no expectation of closure) or surgical intervention. The optimal surgical approach involves resection of the fistulous tract with end-to-end anastomosis (4). If the involved segment of bowel cannot be isolated because of dense adhesions, it may be necessary to perform a bypass procedure, or, occasionally, to divert the fecal stream proximal to the fistula (1,4). If the fistulous tract is embedded in tumor and a radical resection is not feasible, the fistula tract may be defunctionalized by dividing the involved bowel segment proximal and distal to the fistula with a stapling device and performing an end-to-end anastomosis between the proximal and distal limbs of the normal bowel. Fistula drainage is thus reduced to the small volume of mucous and intestinal secretions produced by the isolated segment of bowel containing the fistula (8). There are also reports of a successful “extraabdominal” approach to fistula closure in a small series of patients with dense adhesions or irradiated tissue (9). Finally, the infusion of fibrin glue into lowoutput fistula tracts has been reported to significantly reduce the time to closure; however, this approach is not appropriate for high-output fistulas (10).

Palliative Fistula Management

In the patient with advanced malignancy, neither spontaneous closure nor surgical correction of the fistula may be achievable or practical. In this case, therapy is directed toward maintenance of patient comfort via containment of drainage and odor, protection of the perifistular skin, and continued attention to fluid-electrolyte balance, nutritional support, and control of sepsis (1,5).

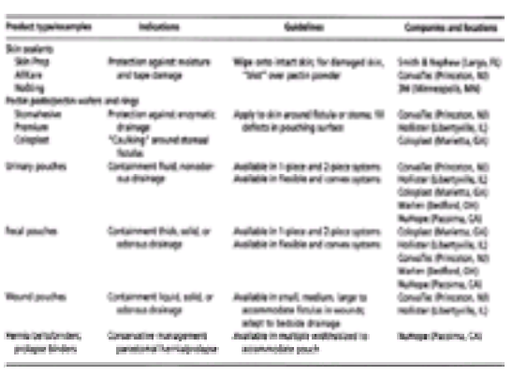
A major component of effective fistula management is containment of the effluent and odor and protection of the surrounding skin; these aspects of care have a profound impact on the patient's quality of life (5). Today, fistulas are treated as spontaneously occurring stomas, and ostomy pouches and products are used to protect the skin while containing the drainage and odor. In addition to promoting the patient's psychological and physical comfort, an effective pouching system permits quantification of output, which is critical to accurate replacement of fluid losses (1,4).

Guidelines for Pouching

Many products and techniques are now available for use in containing the drainage and odor and protecting the perifistular skin. Selection is determined by the type and volume of drainage, the contours of the surrounding tissue, and the integrity of the perifistular skin (1). Additional factors to be considered include the cost and availability of products, the technical difficulty of the procedures compared to the caregiver's cognitive abilities and technical skills, and the availability of professional assistance [e.g., Wound Ostomy Continence (ET) nurses and home care nurses].

Products for Skin Protection

The volume and characteristics of the effluent dictate the level of skin protection required. Drainage that contains proteolytic enzymes or that is highly alkaline or acidic can produce rapid and severe skin breakdown (especially if the fistula is also high-output). Thus gastric, pancreatic, and small bowel fistulas require aggressive protection of all perifistular skin and effective containment of the drainage, if at all possible (1). In contrast, drainage from the colon is usually low volume and nonenzymatic; severe skin breakdown is unlikely, and containment is needed more for odor control than for skin protection. Products available for skin protection include plasticizing skin sealants, pectin-based pastes and wafers, and moisture barrier ointments. The indications and guidelines for use of each of these products are outlined in Table 24-2.



Product type/examples	Indications	Guidelines	Companies and locations
Skin sealants			
Skin Prep All Kare Nu-Stay	Protection against moisture and tape damage	Wipe onto intact skin; for damaged skin, "blot" over pectin powder	Smith & Nephew (Largo, FL) ConvaTec (Princeton, NJ) 3M (Minneapolis, MN)
Pectin pastes/pectin wafers and rings			
Stomahesive Premium Coloplast	Protection against enzymatic drainage "Caulking" around stomal fistulae.	Apply to skin around fistula or stoma; fill defects in pouching surface	ConvaTec (Princeton, NJ) Hollister (Libertyville, IL) Coloplast (Marietta, GA)
Urinary pouches	Containment fluid, nonodorous drainage	Available in 1-piece and 2-piece systems Available in flexible and convex systems	ConvaTec (Princeton, NJ) Hollister (Libertyville, IL) Coloplast (Marietta, GA) Marlen (Bedford, OH) Nu-Hope (Pacoima, CA)
Fecal pouches	Containment thick, solid, or odorous drainage	Available in 1-piece and 2-piece systems Available in flexible and convex systems	Coloplast (Marietta, GA) Hollister (Libertyville, IL) ConvaTec (Princeton, NJ) Marlen (Bedford, OH) Nu-Hope (Pacoima, CA)
Wound pouches	Containment liquid, solid, or odorous drainage	Available in small, medium, large to accommodate fistulae in wounds; adapt to bedside drainage	ConvaTec (Princeton, NJ) Hollister (Libertyville, IL)
Hernia belts/binders, prolapse binders	Conservative management parastomal hernia/prolapse	Available in multiple widths/sizes to accommodate pouch	Nu-Hope (Pacoima, CA)

TABLE 24-2. PRODUCTS COMMONLY USED FOR POUCHING/SKIN PROTECTION

Pouching Principles

As stated earlier, effective containment of drainage and odor is best accomplished via successful application of an adherent pouching system, similar to the systems used to contain ostomy output. Successful pouch application requires adher ence to the following principles: The pouching system selected should be compatible with the type of drainage; the pouching system must be applied to a dry skin surface; and the surface of the pouching system must “match” the perifistular skin contours (1).

In selecting a system that is compatible with the type of drainage, the clinician should assess the effluent for fluidity and odor. Output that is very fluid and relatively nonodorous can be effectively managed with pouches designed for urinary stomas. These systems are odor-resistant (but not completely odor-proof) and equipped with narrow drainage spouts that cannot accommodate thick effluent. Output that is thick or malodorous should be managed with either fecal pouches or wound drainage systems. These systems are odor-proof and are equipped with tapered openings that permit drainage of thick or solid drainage.

As noted, it is essential to assure a dry pouching surface to obtain a good seal between the pouch and the skin. Denuded and weeping perifistular skin interferes with adhesion; unfortunately, perifistular skin damage is common due to the corrosive nature of the drainage. Weeping skin can be treated by a procedure commonly known as *crusting*. A pectin-based powder [Stomahesive Powder by ConvaTec (Princeton, NJ) or Premium Powder by Hollister (Libetyville, IL)] is sprinkled onto the wet skin to absorb the drainage and create a “gummy” surface; the powder is then “sealed” to the skin by blotting over the powder with a moist gloved finger or an alcohol-free skin sealant [e.g., Skin Prep No Sting by Smith and Nephew (Largo, FL), or No Sting by 3-M (Minneapolis, MN)] (1).

Matching the contours of the pouching system to the patient's skin surface is accomplished by carefully evaluating the perifistular skin with the patient in both the supine and sitting positions, and then selecting a pouch that is compatible with those contours. If the perifistular contours are fairly smooth, almost any system can be

used. However, the patient with deep creases in the perifistular skin usually requires an all-flexible pouching system that will “bend and mold.” If the fistula is in a “valley” and the perifistular contours are concave, a convex pouching system is advantageous. It is frequently necessary to use “filler” products such as pectin paste or pectin barrier strips to fill small defects and create a smoother pouching surface (1).

Pouching Procedures

Most fistulas can be managed with a standard pouching procedure using either a standard ostomy pouch or a wound drainage pouch. The standard pouching procedure is outlined in Table 24-3.

Select an appropriate pouch based on type of drainage and abdominal contours.
Size the pouch opening appropriately:
  For fistulas or skin-level stomas, size the opening to clear the fistula/stoma margins by 1/8–1/2 in.; this helps to prevent tunneling of the drainage under the barrier and pouch.
  For protruding stomas, size the opening 1/8 in. larger than the stoma.
Treat any skin damage with skin barrier powder (“seal” with damp finger or skin sealant).
Use pectin paste to fill any surface defects and to “caulk” around the stoma or fistula opening (a wet finger facilitates paste application).
Press pouch into place and use gentle pressure to assure adherence.
Change pouch every 5–7 d and as needed (for leakage).

TABLE 24-3. STANDARD POUCHING PROCEDURE

In patients with very irregular abdominal contours or a large associated wound, the standard pouching procedure is frequently ineffective. One pouching procedure that is frequently effective when standard pouching fails is the trough procedure; however, it is important to note that this technique is appropriate only for fistulas located in open wounds. The basic concept is to protect the perifistular skin with overlapping strips of a skin barrier such as Stomahesive and a pectin-based paste, and then to place transparent adhesive dressings [such as OpSite by Smith and Nephew (Largo, Florida)] over the wound to seal the wound edges. At the most inferior aspect of the wound, a large opening is created in the transparent adhesive dressing, and a pouch is placed over this opening (1). The wound thus becomes a trough, with drainage funneled to the bottom of the wound, where it is collected. Suction can be added to this system for very high-output fistulas. The trough procedure is outlined in Table 24-4 and illustrated in Figure 24-1.

Treat any damaged skin with skin barrier powder (“seal” with damp finger or skin sealant).
Cut skin barrier strips and apply overlapping strips along periphery of wound. Use pectin paste to caulk the junctions between strips and to protect any exposed skin. Note: The strip placed along the inferior aspect of the wound should be a solid U-shaped strip with no overlapping junctions to prevent leakage.
Select transparent adhesive dressing strips that are approximately 4 in. longer than the widest point of the wound; this assures a 2-in. overlap onto intact skin on each side of the wound bed.
Modify one strip of transparent adhesive dressing as follows:
  With paper backing still in place, cut an opening in the dressing wide enough to encompass the inferior aspect of the wound (if wound diameter is 1 1/2 in. at the inferior aspect, the opening should be cut at least 1 1/2 in. in diameter).
  Select a one-piece ostomy pouch or wound pouch and cut an opening in the pouch that matches the opening in the adhesive dressing.
  Peel paper backing off the pouch and stick the pouch to the nonadhesive surface of the transparent adhesive dressing strip
Peel paper backing off transparent adhesive dressing strip with pouch attached and apply to the inferior aspect of the wound
Apply remaining strips of transparent adhesive dressing in overlapping fashion to cover the remaining area of the wound.

TABLE 24-4. TROUGH PROCEDURE FOR FISTULA MANAGEMENT

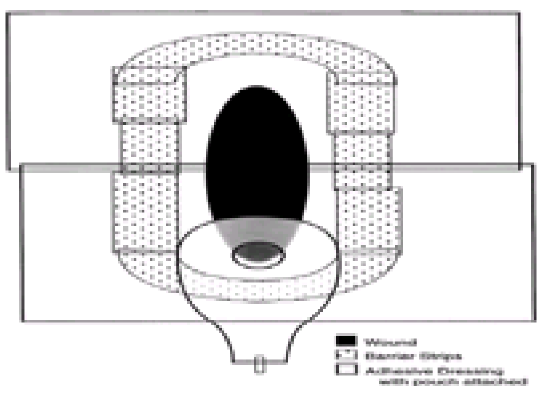


FIGURE 24-1. Illustration of trough procedure for fistula management.

An alternative to the trough procedure for bedbound patients is the closed suction method of management. With this approach, the perifistular skin is again protected with overlapping strips of a skin barrier and skin barrier paste; the wound bed is then lined with a layer of damp gauze and suction catheters are placed over the gauze inferior to the fistulous opening(s). Transparent adhesive dressings are then used to seal the wound on all sides, and the suction catheters are connected to wall suction.

If all pouching procedures fail, or if the caregiver is unable to manage a pouching system, the focus becomes skin protection and odor control. Skin protection can be provided in one of two ways: either by placing overlapping strips of skin barrier along the wound edge, or by applying a thick layer of a zinc-oxide-based moisture barrier along the wound edges. Absorptive dressings are then used to absorb the effluent; these dressings are best secured with a nonadherent system (e.g., burn netting), which facilitates frequent dressing changes. Odor control can be provided by charcoal cover dressings or by oral deodorants (e.g., chlorophyllin copper complex 100 mg once or twice daily). See Table 24-5 for odor control options.

Product type/examples	Mechanism of action	Indications/guidelines for use	Companies and locations/contact information
Odor absorbing dressings: Odor Absorbing Dressing (Hollister); CarboFlex Odor Control Dressing (ConvaTec)	Dressing is impregnated with charcoal; when used as cover dressing, odor molecule forced through charcoal for odor elimination	Indicated for odor control with fistulas being managed with dressings as opposed to pouch; Use as cover dressing, secure on all 4 sides with tape	Hollister (Libertyville, IL) (800-323-4060); ConvaTec (Princeton, NJ) (800-325-8005)
Pouch deodorants: M9 Deodorizing Drops (Hollister); OAD (Coloplast); Marlen Deodorizer; Ostopure (Nu-Hope); Commercial mouthwash	Reduce or neutralize odors in pouches to minimize odor when pouch opened for drainage or replacement	Fecal stomas; Malodorous wounds or fistulas being managed with pouching	Add recommended amount to pouch each time pouch is emptied OR saturate cotton ball with deodorizer and add to pouch each time pouch is emptied
Room deodorants: REFRESH (Cymed); Hex-On (Coloplast)	Reduce or neutralize odors in air; for use when pouch emptied or changed	Spray into air just before opening pouch	Cymed (Berkeley, CA) (800-582-0707); Coloplast (Marietta, GA) (800-533-0464)
Internal deodorizers: Devrom (Bismuth Subgallate), Parthenon Co.; Derifil (Chlorophyllin Copper Complex), Rystan	Significantly reduce or eliminate fecal odor when taken orally on routine basis	Fecal stomas and fistulas; Follow guidelines for dosage and administration; available over the counter	Parthenon Co. (Salt Lake City, UT) (800-453-8898); Rystan (Little Falls, NJ) (973-256-3737)

TABLE 24-5. OPTIONS FOR ODOR CONTROL

Vaginal Fistulas

One type of fistula that cannot be managed by pouching is the vaginal fistula. Patients with rectovaginal fistulas may be managed most effectively by keeping the stool formed to minimize fecal contamination of the vagina. Patients with vesicovaginal fistulas frequently can be managed effectively by placement of an indwelling urethral catheter to decompress the bladder. Patients with enterovaginal fistulas and patients with combined vesicovaginal fistulas, however, require containment to prevent significant perineal skin breakdown. An effective approach for these patients is outlined in Table 24-6.

Perform a vaginal examination to determine the size of the vaginal vault [use a topical anesthetic such as viscous lidocaine (Xylocaine) if patient has significant tenderness].
Obtain a soft rubber *nipple* shield or baby nipple (depending on size of vault) and a mushroom catheter.
Cut a small hole in the tip of the nipple or nipple shield; thread the catheter through so that the mushroom tip is resting within the nipple or shield. Secure the catheter to the nipple or shield with waterproof tape.
Fold the nipple shield down around the catheter, lubricate the nipple shield generously with a water-soluble lubricant, and gently push it into the vagina until the entire shield is in the vault; gently pull back on the catheter until the nipple shield is seated at the vaginal orifice.
Connect open end to bedside drainage unit.

TABLE 24-6. VAGINAL FISTULA MANAGEMENT

Resources

Any patient with a significant fistula can benefit from referral to a Wound Ostomy Continence/ET nurse specialist. These nurses specialize in the management of patients with complex wounds and stomas. Information regarding availability of these specialists can be obtained from the national office of the Wound Ostomy Continence Nursing Society (888-224-9626) or from their Web site (www.wocn.org).

STOMA MANAGEMENT

Urinary or fecal stomas may be created in conjunction with surgical removal of the bladder or rectum due to a malignant tumor, or they may be performed for palliative management of advanced disease producing colorectal or ureteral obstruction. Thus palliative care for patients with GI or genitourinary malignancies frequently requires attention to stoma management and maintenance of GI/genitourinary function.

Management of Fecal Diversions

Descending/Sigmoid Colostomy

A descending or sigmoid colostomy is constructed when the rectum or sigmoid colon is removed or bypassed (11,12). The output from a descending/sigmoid colostomy is typically formed stool, and elimination patterns are similar to preoperative bowel patterns for the individual patient. These patients usually have two options for management (13). One option is to wear an odor-proof pouch and to allow evacuation to occur spontaneously. The other option is to regulate bowel elimination via routine colostomy irrigations. The patient is taught to instill 500–1500 ml of lukewarm tap water into the stoma via a cone tip irrigator that prevents bowel perforation as well as backflow of water (11,14,15 and 16). The distention of the bowel stimulates peristalsis, which usually causes evacuation of the left colon within approximately 30 minutes. Evacuation of this bowel segment typically produces approximately 24–48 stool-free hours. Repeated administration of the same stimulus over time tends to "regulate" bowel emptying so that the potential for fecal spillage between irrigations is reduced. The patient who manages his colostomy with routine irrigation usually can wear a simple stoma cover or a stoma cap between irrigations; the stoma cap provides for absorption of mucus and also deodorizes and vents flatus (11,12 and 13).

Management issues for the patient with a descending or sigmoid colostomy include measures to control odor, reduce gas, and prevent or manage diarrhea and constipation (13,14). Routine measures to control odor include maintenance of an intact pouch seal and a clean drainage "spout"; the pouch material is odor-proof, so odor occurs only if there is a break in the seal or if fecal material is left on the drainage spout. Additional odor-control measures include the use of pouch deodorants (or the addition of 1 teaspoon of mouthwash into the pouch each time it is emptied) or administration of oral deodorants (as outlined in Table 24-5) (14,15). Measures to reduce gas include limitation of gas-producing foods, such as broccoli, cabbage, onions, and beans (13,14 and 15). Diarrhea can occur as a result of a viral illness or in response to some chemotherapeutic agents, and is managed similarly to management of diarrhea in the patient with an intact rectum and anus. The patient is counseled to remain on a low-fat, low-roughage diet; to increase fluid intake; and to take over-the-counter antidiarrheal medications if desired (13,14 and 15). The patient who manages with routine irrigation is instructed to omit irrigations until bowel function and stool consistency return to normal. Constipation is much more common than diarrhea in the patient with advanced malignancy and a descending/sigmoid colostomy; this is due to the antiperistaltic effects of reduced fiber intake, reduced activity, and increased use of analgesics, a triad common in the setting of advanced disease. Acute constipation can be alleviated by the administration of laxative agents (e.g., bisacodyl, milk of magnesia, or polyethylene glycol preparations) or cleansing irrigations. Constipation should also trigger adjustments in the patient's management program: Key elements in an effective program include assurance of adequate fiber and adequate fluid intake (i.e., 28–30 g fiber/day and 30 cc fluid/kg body weight/day). If the patient is unable or unwilling to ingest adequate amounts of dietary fiber, he or she should be counseled to begin a bulk laxative (e.g., Metamucil, Citrucel, Konsyl, PerDiem Fiber) or a bran mixture (1 cup miller's bran plus 1 cup applesauce plus onefourth cup prune juice) at an initial dose of 2 tablespoons/day. The patient is instructed to increase the daily dose by 1 tablespoon each week until normal bowel patterns are reestablished. The patient must be cautioned regarding the critical importance of sufficient fluid intake and the risk of bowel obstruction if bulking agents are consumed without adequate fluids (17,18). If the patient is unable to maintain adequate fluid intake, bulking agents should be discontinued and the patient should be placed on a softener/stimulant combination, such as docusate and casanthranol (17).

Transverse Colostomy

A transverse colostomy may be performed to provide fecal diversion in the patient with distal obstruction. Fecal output from the transverse colon is generally mushy in consistency, and the patient typically experiences output after meals and at other unpredictable times (14). Unlike the descending/sigmoid colostomy, a transverse colostomy cannot be regulated by routine irrigation because of continuous peristalsis in the ascending colon. Therefore, these patients must wear an odor-proof pouch to collect the stool. Management issues for these patients include odor and gas control and management of diarrhea (as discussed in the section Descending/Sigmoid Colostomy) (14). Constipation usually does not occur because the stool in the transverse colon is quite soft and peristalsis in the ascending colon is fairly continuous.

Ileostomy (or Ascending Colostomy)

An ileostomy is most frequently done when the entire colon and rectum are removed for disease processes such as familial polyposis, multiple colonic tumors, or inflammatory bowel disease (11,12). Cecostomies and ascending colostomies are not usually performed but occasionally are required to relieve acute obstruction of the distal ascending or proximal transverse colon (12). Output from these stomas is a thick liquid that contains proteolytic enzymes, which are extremely damaging to the skin (11,14). Management must therefore include continuous pouching with a well-fitting pouch and meticulous skin care to prevent fecal contact with the peristomal skin.

Ascending Colostomy

Management issues for the patient with an ascending colostomy include skin protection, maintenance of fluidelectrolyte balance, and medication modifications (14). The patient is taught to size the pouch carefully to fit closely around the stoma and to protect any exposed skin with pectin-based paste. Patients are also taught to maintain a daily fluid intake of approximately 2 l and to aggressively replace fluids and electrolytes during periods of increased loss (e.g., diarrhea or heavy perspiration); a practical recommendation is to drink a glass of replacement fluid (such as vegetable juice, broth, or a sports drink) each time the pouch is emptied. The patient is taught to recognize signs and symptoms of fluid-electrolyte imbalance and to report such symptoms promptly to the physician (11,14). Medication modifications include avoidance of time-released and enteric-coated medications because these forms are likely to be incompletely and unpredictably absorbed as a

result of reduced bowel length and transit time (14).

Ileostomy

The issues of skin protection, fluid-electrolyte balance, and medication modification are equally critical to the patient with an ileostomy. In addition, the ileostomy patient must be taught how to modify his or her diet to prevent food blockage (11,12,14,19). Food blockage is a complication unique to the ileostomy patient: It occurs when a bolus of fibrous undigested food obstructs the lumen of the bowel at the point where the bowel is brought through the fascia-muscle layer (a point of potential narrowing). Patients with ileostomies are taught to add high-fiber foods (e.g., raw fruits and vegetables, coconut, popcorn, nuts, etc.) to their diets one at a time and in small amounts, to chew thoroughly, and to maintain adequate fluid intake. They are also taught to recognize and report signs of partial or complete blockage (i.e., high-volume malodorous liquid output or no output, coupled with abdominal cramping, distention, and possibly nausea and vomiting) (11,14,15). Food blockage is managed by ileostomy lavage performed by the physician or ostomy nurse specialist. A catheter is inserted into the stoma until the blockage is reached and 30–50 ml of warm saline is instilled. The catheter is then removed to allow for returns, and the procedure is repeated until the blockage is removed (11,14,15).

Continent Fecal Diversions

Most continent fecal diversions are performed for nonmalignant conditions affecting the colon, such as familial polyposis and ulcerative colitis (11,20). These patients, however, are not immune to other malignancies that may progress to an advanced state, and their care must include management of the continent diversion.

Continent Ileostomy

A continent ileostomy (also known as *Koch Pouch* or *Barnett Continent Ileal Reservoir*) differs from a standard ileostomy in that an internal reservoir is constructed between the proximal bowel and the abdominal stoma. The diversion is made continent by intussuscepting the segment of bowel between the reservoir and the abdominal stoma, thus creating a one-way valve (11,12,15,20,21). The patient drains the reservoir by intubating the stoma with a largebore catheter approximately three to four times daily. If the stool is too thick to drain readily, the patient is taught to instill tepid water through the catheter into the reservoir to fluidize the stool (19,20). Management issues include avoidance of foods with peels (because the peels tend to obstruct the drainage catheter) and medication modifications. In addition to avoiding enteric-coated and timereleased medications, these patients must avoid wax-matrix medications because the wax shells do not dissolve and cannot be drained through the catheter. Patients are also instructed to flush the reservoir until clear one or two times daily to prevent pouchitis, an inflammation of the reservoir thought to be caused by bacterial overgrowth (15,20).

Ileal-Anal Reservoir

An ileal-anal reservoir is performed in conjunction with a colectomy and proctectomy. The sphincter mechanism is preserved. A reservoir is then created from the distal small bowel, and anastomosed to the anal canal (20,22). The patient's own sphincter therefore serves as the continence mechanism. The patient with an ileal-anal reservoir has mushy stools with residual enzymes; therefore, meticulous skin care is essential at all times and is even more critical during episodes of diarrhea (20,21,23). The ileal-anal patient is also at risk for pouchitis; symptoms include burning, itching, bleeding, and fecal urgency, and treatment typically involves clear liquids and antibiotics (e.g., ciprofloxacin and metronidazole) (20,22,23).

Management of Retained Nonfunctional Distal Bowel Segment

Patients with a loop or double-barrel colostomy and patients with a Hartmann's pouch have a variable length of distal bowel that is nonfunctional. This segment continues to produce mucus, and some patients require periodic lowvolume rectal enemas to eliminate inspissated mucus (24). It is also relevant to note that medications can be administered rectally even when the rectum is no longer in continuity with the proximal bowel.

Management of Urinary Diversions

Urinary diversions are required for patients with pelvic malignancies necessitating removal of the bladder and for patients with ureteral obstruction that cannot be managed with internally placed ureteral stents. The standard diversion previously was the intestinal conduit, but the current trend is toward construction of continent diversions or orthotopic neobladders anastomosed to the urethra (25).

Intestinal Conduits

Ileal conduits and other intestinal conduits normally produce clear urine with strands of mucus (because a bowel segment is used as the conduit for urinary drainage). Because there is no reservoir for urine collection, urine drainage is almost continuous, and patients must wear a pouch to contain the output (14,26). The most important management issues are prevention and recognition of urinary tract infections. Patients are taught to maintain adequate fluid intake and to recognize and promptly report signs of infection. Confirmation of urinary tract infection and organism identification are usually accomplished by obtaining a catheterized specimen for culture and sensitivity; these data provide the basis for organism-specific treatment (14).

Ureterostomy

Ureterostomies are rarely constructed because of the numerous associated complications (e.g., ineffective drainage, stenosis, and pouching problems). However, these diversions are occasionally required when it is not feasible to construct an ileal conduit. Output from a ureterostomy is clear urine without mucus, and management is the same as for patients with intestinal conduits. In addition, these patients need to be monitored for evidence of stenosis (i.e., reduced output, flank pain, chronic urinary tract infections). Stomal dilatation or stoma revision may be required for management (14,27).

Continent Urinary Diversions

The trend in urinary diversions is construction of continent reservoirs. A variety of surgical procedures exist, but all involve construction of a low-pressure reservoir; an antireflux mechanism between the reservoir and the ureters; and a continent, catheterizable channel between the reservoir and the abdominal surface (20,25,26). The two most commonly performed are the Koch Urostomy and variations of the ileocecal reservoir (e.g., Indiana Reservoir, Florida Pouch, and Miami Pouch) (20,28). Normal output is clear urine with strands of mucus; long-term management involves intermittent intubation and irrigation of the reservoir (with water or saline) to remove the mucus and prevent pouchitis (20). Adequate fluid intake and close adherence to the catheterization schedule help to prevent urinary tract infections (20). These patients typically need only an absorptive pad over the stoma, and significant leakage is uncommon. Patients who develop significant leakage usually are managed by using two-piece pouching systems. This provides for containment of the urinary leakage while maintaining ready access to the stoma for routine catheterizations. (Routine catheterization must be continued to prevent urinary retention and resultant infection.)

Orthotopic Neobladder to Urethra

The newest approach to urinary tract reconstruction after cystectomy is construction of a neobladder with anastomosis to the retained urethral sphincter mechanism. This procedure is limited to patients whose malignancy can be resected adequately without compromising the sphincter (20,29). Because the neobladder is usually a noncontractile reservoir constructed from detubularized bowel, effective emptying depends on effective relaxation of the voluntary sphincter in combination with abdominal muscle contraction to increase the pressure in the reservoir (20,29). Patients must be monitored for urinary retention, and patients who are unable to empty the reservoir completely are taught to augment voluntary voids with clean, intermittent catheterization to prevent urinary stasis and resulting infection (20,29). Another common problem is some degree of urinary leakage, particularly at night (when the voluntary pelvic floor muscles are partially relaxed). Depending on the severity of the leakage, absorbent products may be required for containment.

Pouching: Products and Principles

As outlined in the section Fistula Management, the key principles in stoma management include containment of the drainage and odor and protection of the peristomal skin. The degree of skin protection required is dictated by the characteristics of the output. Drainage that is proteolytic or highly acidic or alkaline requires meticulous protection of all peristomal skin, whereas nonenzymatic drainage with a pH that is essentially neutral primarily requires protection against pooling of drainage and subsequent maceration (14). Thus, ileostomies and ascending colostomies require aggressive skin protection, whereas descending/sigmoid colostomies and urinary diversions primarily require protection against prolonged contact between the drainage and the skin.

Products available for protection of peristomal skin include skin sealants, skin barriers, and pectin-based paste. The use of these products is outlined in Table 24-2. As mentioned earlier, pouching systems are available for both urinary and fecal drainage. Pouching systems are also available as both one-piece and two-piece systems.

One-piece systems typically are constructed with a barrier ring and tape border to which the pouch is welded, and are available in both precut and cut-to-fit varieties. Two-piece pouches typically consist of a barrier wafer to which a raised flange is attached and a pouch with a matching gasket that is snapped onto the flange (14,15). Application guidelines are the same as those for fistula pouch application (Table 24-3).

Management of Peristomal Complications

Common peristomal complications include epithelial denudation, monilial rash, and allergic reactions to ostomy products. Prompt recognition and appropriate intervention usually result in complete resolution of the problem.

Denudation

Superficial skin loss in the peristomal area is usually caused by a poorly fitting or incorrectly sized pouch that allows the effluent to contact the peristomal skin. The area of damage typically extends from the stoma along the path taken by the effluent; the area is usually red, raw, and painful (27,30). The most important intervention is correction of the underlying problem (i.e., modification of the pouching system). Actual treatment of the denuded areas involves application of a pectin-based powder [e.g., Stomahesive by ConvaTec (Princeton, NJ) or Premium by Hollister (Libertyville, IL)] to the denuded areas; the powder can then be "sealed" by blotting with a moist finger or an alcohol-free skin sealant [e.g., No Sting by 3M (Minneapolis, MN) or Skin Prep No Sting by Smith and Nephew (Largo, FL)]. Severely denuded areas may require several layers of powder and sealant to provide a thick protective layer. The correctly sized pouching system can then be applied over the treated surface (27).

Monilial Rash

Peristomal yeast rashes can occur as a result of antibiotic administration with resulting overgrowth of yeast organisms in the bowel, or as a result of constant moisture resulting from a leaking pouch or heavy perspiration under the plastic pouch material. The rash has a maculopapular appearance with distinct border (satellite) lesions and is commonly pruritic. It usually responds promptly to nystatin powder dusted onto the peristomal surface and then blotted with a skin sealant or moist finger to create a dry or sticky pouching surface (14,15,27).

Allergy

Any product used to protect the peristomal skin or to contain the output can be an allergen. Allergic contact dermatitis is typically characterized by an area of erythema that corresponds to the skin surface exposed to the allergen. The patient typically describes the area as pruritic and tender, and vesicles may be noted with severe reactions (15,27). The first step in management is to identify and eliminate the allergen, which can be a challenge when the patient is using a variety of products on the involved skin. Usually the distribution of the reaction helps to identify the offender, although patch testing may be required when the identity of the allergen is unclear (14,27). Until the specific allergen is identified and the peristomal skin has normalized, product use should be minimized; for example, use of paste, powder, and sealants should be eliminated if possible, and the patient should be managed with a solid barrier and pouch (such as a two-piece pouching system with a barrier wafer to which the pouch is attached). Patients with severe blistering or pruritus may require topical or systemic antihistamines or corticosteroids in addition to the measures already identified. If topical products are used, sprays or vanishing gels should be selected because creams and ointments interfere with pouch adhesion (14,15).

Management of Stomal Complications

Although stomal complications are uncommon, they can interfere with normal ostomy function or with effective containment of the output. Therefore, the clinician needs to be knowledgeable regarding their management.

Peristomal Hernia

Peristomal hernia involves herniation of the bowel through the muscle defect created by the stoma and into the subcutaneous tissue (11,15,27). The hernia usually reduces spontaneously when the patient is in a reclining position and intraabdominal pressure is reduced. Problems created by peristomal hernias include the potential for strangulation and bowel obstruction, which is uncommon, and difficulty with maintenance of an effective pouch seal, which is more common (27,30,31). In the patient with advanced cancer, surgical intervention is usually reserved for emergency situations involving strangulation and obstruction (31). Conservative management commonly includes use of a hernia belt, which is an abdominal binder with a cutout that accommodates the stoma and pouch (27,30). The belt is applied while the patient is recumbent and the hernia is reduced, and the resistance provided by the belt helps maintain reduction of the herniated loop of bowel. Colostomy patients who manage their stomas with routine irrigation must be cautioned to irrigate only with a conetip irrigator (because a catheter could cause perforation of the herniated loop) and to instill the irrigation fluid in the recumbent or semirecumbent position (so that the hernia is reduced) (27).

Stenosis

Stomal narrowing to a point that interferes with normal function can occur at either the skin level or the fascia level (30). Stenosis at the skin level may be evidenced by visible narrowing of the stomal lumen, but stenosis at fascia level can be detected only by digital examination. Signs of stenosis include reduced output, cramping pain, abdominal distention (with fecal diversions), and flank pain or infection (with urinary diversions). Stenosis that interferes with normal function requires surgical revision, either local excision of the stenotic area or open laparotomy (15,27).

Retraction

Early retraction of the stoma to a plane below skin level can occur postoperatively as a result of tension on the bowel or mesentery or due to breakdown of the mucocutaneous suture line. Late retraction can be caused by ascites or intraperitoneal tumor growth causing abdominal distention or tension on the mesentery. Retraction can also be caused by excessive postoperative weight gain (30). Management involves modification of the pouching system to accommodate the change in peristomal contours; typically, a convex pouching system is required (27).

Prolapse

Factors contributing to stomal prolapse include increased intraabdominal pressure, loop stoma construction, location of the stoma outside the rectus muscle, and formation of an excessively large aperture in the abdominal wall (32). Prolapse is usually quite upsetting to patients; however, prolapse does not represent a surgical emergency unless there is evidence of incarceration and stomal ischemia (30,32). Sometimes a prolapsed stoma can be reduced—the patient is placed in a recumbent position to reduce intraabdominal pressure, and manual reduction is attempted (33). (If the stoma is very edematous, a hypertonic substance, such as sugar or salt, may be applied topically to reduce the edema before reduction is attempted.) Once the prolapse is reduced, a hernia belt with prolapse overbelt (or a simple abdominal binder) can be used to prevent recurrence. If this approach fails, surgical intervention may be required (15,27,30).

Bleeding

Slight stomal bleeding during pouch changes is common due to the vascularity of the stoma. However, significant or spontaneous bleeding is not normal and requires investigation and intervention. Bleeding from the stoma itself usually can be managed by direct pressure, application of ice, or silver nitrate cauterization (27). Bleeding originating from the bowel requires further work up, with intervention determined by the causative factors and the patient's overall status (27).

Specific Issues for Oncology Patients

Some specific ostomy-related issues are relevant only to cancer patients. These issues include management of a stoma in the radiation field, management of stomatitis, and the impact of advancing disease on selfcare and management.

Stoma in Radiation Field

The goal in management of a stoma in the radiation field is to prevent peristomal skin damage. If the radiation oncologist wishes to have the pouch removed for each treatment, the patient should be switched to a nonadhesive pouching system [e.g., Hollister one-piece Karaya (Libertyville, IL) ring pouches with belt attachment or Cook (Wound Ostomy Continence, Spencer, IN) nonadhesive pouches] (34). If the radiation oncologist elects to leave the pouch in place during treatments, the pouching system should be modified to eliminate any metallic agents that could cause scatter of the radiation beam at skin level (e.g., tapes containing zinc oxide) (34). Pectin-based barriers, plastic pouches, and porous paper tape are all safe for peristomal use. Any peristomal damage that does occur can usually be managed by

applying a hydrocolloid wafer dressing [e.g., DuoDerm by ConvaTec (Princeton, NJ)] to the peristomal skin under the pouch.

Management of Stomatitis

Stomatitis, a common side effect of both radiation therapy and chemotherapy, is manifested by stomal edema, vasocongestion, and possibly ulceration. The goals of treatment are to prevent secondary infection and to prevent trauma and bleeding. Colostomy patients who manage their stomas with routine irrigation are instructed to omit irrigation during courses of pelvic radiation and during any episodes of stomatitis caused by chemotherapy (34). Patients also are counseled to avoid vigorous cleansing of the stoma and, if the stoma is friable, may be advised to add small amounts of mineral oil to lubricate the inside of the pouch (once radiation is complete). Patients with continent diversions may need to use smaller catheters, additional lubricant, and extreme caution in intubating the reservoir. Patients who develop stomatitis secondary to chemotherapy usually require treatment with antifungal agents (35) because the entire length of the alimentary canal is likely to be affected.

Impact of Advancing Disease on Self-Care and Management

One of the most significant issues facing the ostomy patient with advanced disease is selfcare and management. It is frequently necessary to modify the patient's management regimen or to teach a family member to change the pouch or intubate the stoma as the patient becomes less able to manage his or her own care. The colostomy patient who has managed with irrigation and who is no longer able to perform this procedure needs to be placed on a drainable pouching system. As noted earlier in this chapter, constipation is a common problem for the colostomy patient with advanced cancer, but usually can be managed with bulk and stimulant laxatives, stool softeners, and irrigations as needed (36). Removal of impacted stool usually can be accomplished by administration of a 1:1 solution of milk and molasses given as an irrigation.

The patient with a continent urinary diversion (or orthotopic neobladder) may be managed by insertion of an indwelling catheter into the reservoir if to do so is more feasible for the caregiver than intermittent intubation. The caregiver should be instructed in once or twice daily irrigations to eliminate retained mucous.

The home health or hospice nurse can be extremely valuable in assisting the patient and family to modify their care routines in the most effective and manageable way.

SUMMARY

Effective management of fistulas and stomas requires containment of drainage and odor plus protection of the surrounding skin. These aspects of care have a significant impact on the quality of life for patients with advanced disease.

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25

MANAGEMENT OF DYSPNEA

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Dyspnea has been defined as an uncomfortable awareness of breathing (1). Although everybody has experienced the sensation and has an intuitive understanding of this symptom, there is no universal agreement as to its definition. Dyspnea is a subjective sensation and cannot be defined by the physical abnormalities that accompany such unpleasant subjective experience. For the purpose of this chapter, dyspnea is defined as an unpleasant sensation of difficult, labored breathing.

Dyspnea is a frequent and devastating symptom in patients with advanced cancer (2,3). It has been reported to occur in 21–79% of advanced cancer patients (4). There is evidence that good symptom control, even by experienced palliative care teams, is achieved less frequently for dyspnea than for other symptoms such as pain or nausea (5). In addition, limited research and education are available on the adequate assessment and management of dyspnea in cancer patients.

The aim of this chapter is to review the pathophysiology, prevalence, assessment, and treatment of dyspnea in cancer patients. Discussion of areas where future research should focus is also included.

PATHOPHYSIOLOGY

Dyspnea is frequently associated with abnormalities in the mechanisms that regulate normal breathing. However, the actual expression of dyspnea by a patient results from a complex interaction between the abnormalities in breathing and the perception of those abnormalities in the central nervous system. The origins of dyspnea in different clinical settings can be traced to specific abnormalities. These are discussed in the following paragraphs.

Regulation of Breathing

Figure 25-1 summarizes the regulation of normal breathing. Respiration is integrated as a system with three main components, as discussed in the following sections.

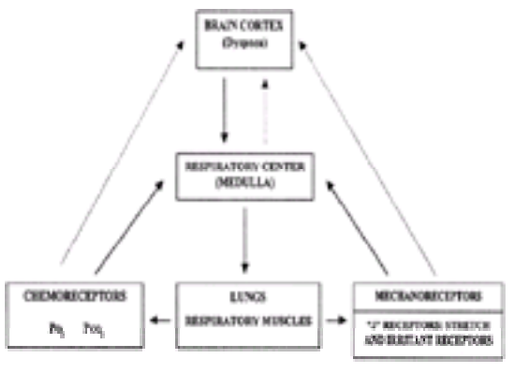

FIGURE 25-1. Regulation of normal breathing.

Respiratory Center

The respiratory center is located in the medulla. Its neurons receive information from both central and peripheral chemoreceptors and peripheral mechanoreceptors. It also receives information from the cerebral cortex, which regulates voluntary breathing such as occurs during speaking and singing. Efferent neurons stimulate the diaphragm, the intercostal muscles, and the accessory muscles (6,7).

Receptors

The levels of oxygen and carbon dioxide in the blood stimulate chemoreceptors located both centrally and peripherally. These chemoreceptors are capable of stimulating the respiratory center and increasing respiratory rate (8,9). Although strong debate continues on this subject, recent evidence suggests that chemoreceptors are probably also able to stimulate the brain cortex directly and cause dyspnea (9). An alternative explanation for the dyspnea caused by increases in PCO_2 and decreases in PO_2 is that chemoreceptors stimulate the respiratory center; increasing the respiratory effort, which stimulates mechanoreceptors capable of stimulating the brain cortex, resulting in the sensation of dyspnea. The mechanoreceptors are located primarily in the respiratory muscles and the lung. These receptors respond to either irritants or, more commonly, pulmonary stretch, including vascular congestion (7).

Respiratory Muscles

The respiratory muscles promote gas exchange. Changes in the PO_2 and PCO_2 are detected by the chemoreceptors. Changes in the tension within the abdominal wall and the lung are detected by the mechanoreceptors. This information is fed back to the respiratory center. Sensory receptors are found inside the respiratory muscles, including the intercostal, sternomastoid, and diaphragm. The balance between the contractual activity and stimulation of the sensory receptors is of great importance in the type of input provided to the respiratory center and the cortex.

Although the three aforementioned factors are the main elements in the regulation of breathing, the actual sensation of dyspnea is a result of cortical stimulation. The sensation of dyspnea has been related to the activation of mechanoreceptors in the respiratory muscles and lung (10). Elegant research has shown that both in normal volunteers and patients, different stimuli capable of stimulating mechanoreceptors are able to produce dyspnea even in absence of increased respiratory activity (7,8). In addition, two other possible mechanisms of dyspnea have been proposed. On one hand, the previously discussed role of chemoreceptor stimulation, on the other hand, some authors have proposed a role for the respiratory center as a potential cause of dyspnea by direct ascending cortical stimulation (8,9,11).

Production of Dyspnea

Dyspnea is produced by physical and biochemical abnormalities (Fig. 25-2). The perception is then modulated by anxiety, depression, or administration of opioids. Somatization and cultural factors further influence a patient's expression of dyspnea.

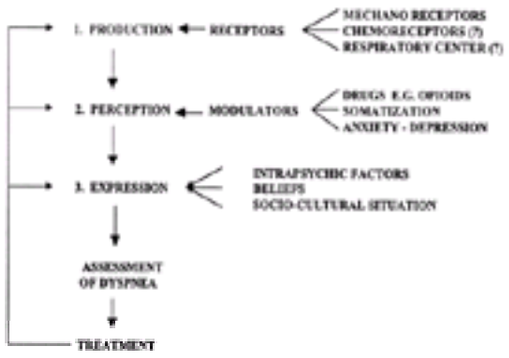

FIGURE 25-2. Stages in the production of dyspnea.

A number of researchers have found great variability in the expression of dyspnea among patients with similar levels of functional abnormalities. Among patients with asthma, approximately 15% did not report dyspnea despite severe airflow obstruction (forced expiratory volume in 1 second of less than 15% of the predicted) (12). Similarly, among patients with chronic obstructive pulmonary disease (COPD), the complaint of dyspnea was not well correlated with abnormalities in the pulmonary function tests (13). Among these patients who were defined as having disproportionate dyspnea (complaint of dyspnea in the presence of a mean forced expiratory volume in 1 second of 1.8 liter), almost all patients were considered to have a psychiatric diagnosis (mostly anxiety and depression) (13). Anxiety has been shown to be an independent correlate of the intensity of dyspnea in cancer patients (14). This association is not entirely clear as anxiety may contribute to dyspnea but may also arise from its presence.

These studies suggest that some patients have modulators that either amplify or decrease the intensity of the symptom that is perceived at the cortical level. Patients receiving drugs such as opioids for pain can perceive significantly less dyspnea (2).

Finally, the expression of a certain symptom may be influenced by cultural factors, the belief about the mechanism for the symptom, and other factors such as somatization (15). Because neither the production nor the perception of dyspnea can be measured at present, the entire assessment is based on the patient's expression. This issue is discussed in the following section.

Clinical Situations Associated with Dyspnea

Dyspnea can result from three main pathophysiological abnormalities (7):

1. An increase in respiratory effort to overcome a certain load (e.g., obstructive or restrictive lung disease, pleural effusion)
2. An increase in the proportion of respiratory muscle required to maintain a normal workload (e.g., neuromuscular weakness, cancer cachexia)
3. An increase in ventilatory requirements (hypoxemia, hypercapnia, metabolic acidosis, anemia, etc.)

In many cancer patients, different proportions of the three abnormalities may coexist, thereby making the pathophysiological interpretation of the intensity of dyspnea more complex.

Role of Respiratory Muscles

During recent years a number of authors have found that respiratory muscle weakness has an important role in the dyspnea associated with a number of chronic conditions. Palange et al. (16) found that malnutrition significantly affected the muscle aerobic capacity and exercise tolerance in patients with COPD. They suggested that high wasted ventilation might be responsible for the weight loss. Diaphragmatic fatigue has been associated with dyspnea in patients with COPD (17). In chronically malnourished patients without pulmonary disease, malnutrition reduces respiratory muscle strength and maximal voluntary ventilation. Therefore, malnutrition might impair the respiratory muscle capacity to handle increased ventilatory loads in cardiopulmonary disease (18). In normal volunteers, the sensation of dyspnea has been correlated with respiratory muscle fatigue (19).

A study in cancer patients determined that the maximal inspiratory pressure, a reliable functional test of the strength of the diaphragm and other respiratory muscles, is severely impaired in cancer patients with dyspnea (20). Maximal inspiratory pressure has subsequently been found to be an independent correlate of intensity of dyspnea in a subgroup of advanced cancer patients with moderate to severe dyspnea (14).

PREVALENCE OF DYSPNEA

The large variation in reported prevalence of dyspnea (21–79%) is a result of the different natures of patient populations reported by different authors and the lack of a general consensus on the assessment methods for identifying and quantifying the presence and intensity of dyspnea.

Higginson and McCarthy (5) conducted a prospective study in 86 consecutive patients with advanced cancer referred to a Community Palliative Care Service. Eighteen patients (21%) reported dyspnea as their main symptom before death. The symptom assessment scores for patients with dyspnea showed no change over time, as compared with a significant decrease in the intensity of pain reported by this same patient population.

Reuben et al. (21) reported on the prevalence of dyspnea in patients admitted to the National Hospice Study. Dyspnea occurred in 70% of 1754 patients sometime during the last 6 weeks of life. The frequency of dyspnea increased during the last weeks of life and more than 28% of patients rated the severity of their symptoms as moderate or worse during the self-report assessment. During the last 6 weeks of life, 27.5% of patients reported dyspnea all the time. Although 33% of patients had the diagnosis of primary or metastatic lung cancer, 24% of patients with dyspnea did not have any known lung or heart disease or evidence of pleural effusion. Grond et al. (22) reported a prevalence of dyspnea of 24% among 1635 cancer patients referred to a pain clinic. Donnelly et al. (23) found dyspnea in 28% of 1000 patients referred for consultation to a palliative care service. Of those patients who reported dyspnea, 63% rated this symptom as moderate or severe.

Twycross and Lack (24) found a prevalence of 51% of dyspnea in 6677 patients admitted to a palliative care program. Muers (25) found breathlessness to be a presenting complaint for 60% of 289 patients with no-small cell lung cancer, half of whom described their shortness of breath as moderate or severe.

A number of authors have reported dyspnea in a significant percentage of advanced cancer patients without intrathoracic malignancy. The National Hospice Study (15) found a frequency of 24% in patients with no known lung or heart disease. Cachexia occurs in more than 80% of patients with advanced cancer (26). In addition, asthenia and electrophysiological abnormalities in muscle function are detected in a large proportion of patients with advanced cancer. A recent study of 222 patients with chronic congestive heart failure found that dyspnea was the exerciselimiting symptom in 160 and generalized fatigue in 62 patients. No significant differences were found between any of the cardiovascular parameters of these two groups. The authors concluded that both symptoms are “two sides of the same coin,” and they express the same underlying pathophysiological process (27). It is possible that in some patients with advanced cancer, dyspnea may be one clinical expression of the syndrome of overwhelming cachexia and asthenia that is highly prevalent in the comprehensive assessment of these patients, including frequent pulmonary function tests.

In summary, dyspnea appears to be a common symptom in patients with advanced cancer. It is reported more commonly in patients during the last weeks of life. Although it is more common among patients with lung cancer or pulmonary metastases, it is also frequent in patients with no demonstrable tumor involvement in the lung. Most patients who develop dyspnea tend to rate this symptom as one of their main problems.

Figure 25-3 summarizes the common causes of dyspnea in cancer patients. Less common causes include dyspnea in cancer patients: atelectasis, phrenic nerve palsy, tracheal obstruction, carcinomatous infiltration of the chest wall, abdominal distention, pneumothorax, and metabolic acidosis. The pathophysiology of dyspnea in most

cancer patients is complex. For example, a given patient may have an increase in respiratory effort necessary to overcome the presence of a large pleural effusion, in addition to an increase in the proportion of respiratory muscle required for breathing because of cachexia and increased ventilatory requirement resulting from severe anemia.

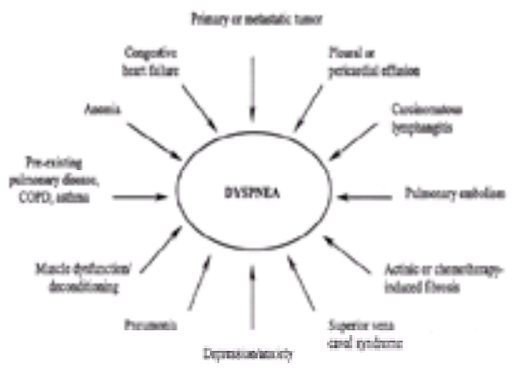

FIGURE 25-3. Common causes of dyspnea in patients with advanced cancer. COPD, chronic obstructive pulmonary disease.

ASSESSMENT

Although most cancer patients develop dyspnea as a progressive complication over days or weeks, some patients present with sudden onset of dyspnea as an acute medical emergency. The management of the latter group always should be considered a medical emergency.

History

The cause of dyspnea can be determined easily in most patients by taking an adequate history and performing a physical examination. The intensity of dyspnea should be assessed using a validated system. An additional approach that could potentially lead to the collection of useful information regarding the pathophysiological basis of dyspnea in individual patients is to look at descriptors of dyspnea.

Intensity of Dyspnea

The expression of the intensity of dyspnea can be assessed using visual analogue, numerical, and verbal scales (28,29,30,31 and 32). The intensity of dyspnea is included in some of the available supportive care tools, such as the Support Team Assessment Schedule (4) and the Edmonton Symptom Assessment System (32). Quality-of-life questionnaires, including the European Organisation for Research and Treatment in Can cer Quality of Life Core Questionnaire, have provided for a more detailed assessment of the intensity of dyspnea in certain modules (e.g., lung cancer) (33).

In addition to these more general questionnaires, some specific dyspnea questionnaires have been developed. The chronic respiratory questionnaire was tested against a number of physical parameters in patients with COPD (34,35 and 36). The Medical Research Council Scale has been tested in patients with dyspnea from a variety of respiratory and cardiovascular origins (37,38). Mahler et al. (39) compared the Medical Research Council Scale with a recently developed baseline dyspnea index and the oxygen cause diagram in 153 patients with various respiratory illnesses who sought medical care because of dyspnea. The authors found correlation between the different dyspnea scores. Agreement between two observers or with repeated use was satisfactory with all three clinical rating methods.

The Borg Category Scale (30,40) was originally developed for rating perceived dyspnea during exercise. It consists of 15 grades, with numbers ranging from 6–20. A more recent modification revised the numbers from 0–10, and the verbal descriptors are placed so that doubling the numerical rating corresponds to a twofold increase in sensation intensity. In addition to these scales, other dyspnea scales have been developed during recent years (41,42). In summary, a large number of scales are available for assessment of the intensity of dyspnea. They range from simple analogue and numerical scales to more complex scales, including multiple items. Many of these scales have been adequately validated and are highly reproducible.

One of the main problems associated with assessment of dyspnea is the variable intensity of this symptom according to the level of activity and during different times of the day. The variation in intensity of dyspnea over time makes pharmacological and nonpharmacological symptomatic interventions difficult to assess. In patients with respiratory and cardiovascular diseases, one approach to this problem has been the performance of dyspnea-causing activities to be able to compare therapeutic interventions (43,44). Most of these interventions consist of progressive exercising on a treadmill or bicycle so that patients or volunteers are subjected to a predictable workload. Dyspnea then is measured at fixed intervals and expressed in relationship to the workload. However, most cancer patients are too ill to participate in these stress tests. One potentially less invasive approach to the production of dyspnea is breath-holding (45,46), which has been used successfully to assess different mechanisms of dyspnea. Immediately after breath-holding, there is a period when no particular respiratory sensation is experienced (20–30 seconds in healthy subjects). This is followed by a second period in which there is progressive discomfort until breaking point. It has been found that training plays an important role in prolongation of total breath-holding time, but has little effect on the period of no respiratory sensation. In addition, the period of no respiratory sensation in patients with COPD is apparently shortened and measurement of this period can be useful in the study of the genesis of dyspnea (47). Breath-holding has not been prospectively validated for use as an assessment tool in cancer dyspnea.

Another potential approach to dyspnea assessment is to use reading to measure the limiting effects of breathlessness. A recent study (48) looked at a simple test involving reading of numbers in 30 cancer patients and 30 controls. Five 60-second readings off a number grid were undertaken on three occasions, two on the same day and one a week later. Patients read fewer numbers, and fewer numbers per breath than controls. Twelve of 30 patients were unable to complete all five readings in all three tests due to tiredness. The test was found to have good repeatability, both within and between days, and was sensitive to improvement seen following drainage of pleural effusions in 13 patients.

Descriptors of Dyspnea

In the case of pain, specific descriptors are associated with specific pathophysiological syndromes (49). For example, a burning or numb sensation traditionally has been associated with neuropathic pain. In many cases, the descriptor alone is enough to make a diagnosis and suggests the need for specific drug therapy. Simon et al. (50) attempted to associate specific descriptors with specific pathophysiology in 53 patients with dyspnea caused by a number of known causes. Patients were asked to choose descriptions of their sensation of breathlessness from a dyspnea questionnaire listing 19 descriptors. Cluster analysis then was used to identify natural groupings among those descriptors.

Although descriptors, such as “rapid” or “heavy,” were associated with exercise, “tight” frequently was associated with asthma, and “suffocating” frequently was associated with congestive heart failure. Mahler et al. (51) used a questionnaire with 15 items that described qualities of breathlessness in 218 patients who sought medical care for breathlessness. The authors concluded that patients with different cardiorespiratory conditions experience distinct qualities of breathlessness and that using a questionnaire containing descriptors of dyspnea might help to establish a specific diagnosis. However, a recent study has suggested that different ethnic groups use different words to describe breathlessness in the presence of airflow obstruction (52). This requires further clarification. In addition, more research is needed to better characterize the quality of dyspnea associated with specific clinical conditions.

Physical Examination and Investigations

A general physical examination with focused attention on the cardiac and respiratory systems is essential. A chest radiograph, digital oximetry, and simple blood tests can help in determining its cause. Pulmonary function tests can be particularly useful in the assessment of obstructive and restrictive pulmonary disorders as well as neuromuscular weakness. These tests can be performed repeatedly at the bedside and are useful in assessing the response to different therapies, in particular bronchodilators. The measurement of maximal inspiratory pressure may also be useful in cancer patients (14).

Multidimensional Assessment

Although some researchers have described a good correlation between the abnormality of pulmonary function tests and the intensity of subjective dyspnea (39), others found this correlation to be extremely poor (42). In some cases, the authors suggested that the lack of correlation between objective and subjective findings might be

due to underlying psychiatric disorders (13).

Figure 25-2 shows the different stages in the production of dyspnea. These are common to other symptoms, such as pain. Neither the production nor perception of dyspnea can be measured. Expression of the intensity of dyspnea can be influenced by a number of factors described in the figure and should not be interpreted as a direct representation of the intensity of production of dyspnea at the level of mechanoreceptors or chemoreceptors.

The complex nature of dyspnea in many cancer patients means that assessment of dyspnea in isolation is inappropriate and may result in over treatment or inappropriate treatment of a patient's expression of dyspnea. Multidimensional assessment of dyspnea using tools that look at dyspnea in the context of other physical and psychological symptoms allows for determination of the part played by other factors such as pain, anxiety, depression, and somatization in the expression of dyspnea. The Edmonton Symptom Assessment System is an example of a validated multidimensional assessment tool (32,53). Identification of the various factors influencing the expression of dyspnea in a given patient allows for the implementation of a multidimensional therapeutic approach for that patient.

TREATMENT

Treatment of dyspnea should focus on a patient's expression of dyspnea rather than his or her apparent level of dyspnea as judged by tachypnea and use of accessory muscles of respiration, or the level of oxygen in the blood. It is not unusual for patients to have marked tachypnea and not report difficulty in breathing or conversely to report severe dyspnea in the absence of tachypnea.

Treatment approaches include therapies aimed at modifying a specific pathophysiologic cause and therapies aimed to provide general symptom control.

Treatments of Specific Pathophysiological Causes

In patients in which a specific cause of dyspnea is suspected, appropriate treatment of the potential underlying cause should be initiated. Treatment modalities include radiation therapy, often accompanied by high-dose corticosteroids for superior vena cava syndrome, and chemotherapy for some patients with pleural effusions or carcinomatous lymphangitis. High-dose corticosteroids may also be useful for patients with the latter. Drainage of pleural or pericardial infusions can give rapid relief. Other procedures, such as pleurodesis or creation of a pericardial window, may be necessary when effusions are recurrent.

Reversible airway obstruction is a common cause of dyspnea in cancer patients who have a history of heavy smoking (56). Optimum treatment of airway obstruction using bronchodilators, corticosteroids, and, if necessary, antibiotics for infective exacerbation of symptoms should be addressed in these patients. In addition, infections including pneumonia are responsible for the deaths of almost half the patients who die with advanced cancer (55). Dyspnea associated with pneumonia can be effectively treated with appropriate antibiotics.

In addition to the aforementioned causes, patients may present with severe anemia, massive ascites, an acute exacerbation of chronic asthma, or acute panic attacks as part of a chronic panic disorder. The latter is characterized by hyperventilation. Occasionally, metabolic acidosis associated with acute renal failure or lactic acidosis can result in hyperventilation. All these diagnoses should be considered during assessment of a patient with dyspnea and advanced cancer because specific therapy may result in rapid symptom relief.

Symptomatic Treatment

Symptomatic management of dyspnea is based on three main elements: oxygen therapy, drug therapy, and general measures of support and counseling. Evidence for the role of these three therapeutic approaches are discussed in subsequent paragraphs. For the purpose of this review, a Medline search of the literature on dyspnea published between 1966–2000 was conducted. All studies relating to the symptomatic therapy of dyspnea were reviewed. Studies were classified according to their methodology in three levels of evidence (56).

Oxygen

Long-term oxygen therapy has beneficial effects on the outcome of patients with COPD (57,58). However, the symptomatic effects of this therapy are less clear. Some studies suggest that oxygen has no symptomatic effects in cancer dyspnea (59,60). In addition, the evidence for a beneficial effect of oxygen in patients with congestive heart failure is also controversial.

Table 25-1 summarizes studies that have addressed the use of oxygen for symptom relief in a number of conditions. Only studies with level 1 evidence (randomized controlled trials) are discussed in this chapter. In the case of COPD, most studies suggest that there is a significant symptomatic improvement at rest and during exercise as a result of the administration of supplemental oxygen (61,62,63 and 64). However, Liss and Grant (65) found that the administration of 0, 2, or 4 liters per minute of oxygen to patients with COPD was not superior to air on resting dyspnea. These authors also found a significant increase in breathlessness after nasal anesthesia with lidocaine. The authors suggested that the reduction in breathlessness caused by nasal oxygen is a placebo effect caused by wearing the nasal canula and is unrelated to gas flow or the increase of arterial oxygen tension. In the case of congestive heart failure, one study found that supplemental oxygen could improve subjective scores for fatigue and breathlessness during steady-state exercise (66). Another study, however, found no significant benefit from supplemental oxygen on the symptomatic scores of patients subjected to regular walking (67).

Author (reference)	No. of patients	Dose O_2	Disease	Findings	Level of evidence[a]
Bruera et al. (60)	14	O_2 5 l/min or air	CAF	+	I
Bruera et al. (59)	1	O_2 5 l/min or air	CAF	+	I (N of 1)
Booth et al. (70)	38	O_2 4 l/min or air	CAF	Both +	I
Swinburn et al. (61)	10/12	O_2 28% 4 l/min or air	ILD/COPD	+/+	I
Liss et al. (65)	8	O_2 28% or air	COPD	-	I
Davidson et al. (62)	17	4 l/min or air	COPD	+	I
Woodcock et al. (63)	10	O_2 28% 4 l/min or air	COPD	+	I
Dean et al. (64)	12	O_2 40% or air	COPD	+	I
Moore et al. (66)	12	O_2 30%, 50% or air	CHF	+	I
Reardon et al. (67)	12	O_2 2 l/min or air	CHF	-	I

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; +, effective; -, not effective.
[a]Medline search from 1966–2000 of studies on the symptomatic treatment of dyspnea.
[a]Level of evidence, I, randomized controlled trial.
[b]Cancer hypoxemia.
[c]Only six patients had hypoxemia.

TABLE 25-1. SYMPTOMATIC EFFECT OF OXYGEN THERAPY[a]

Although the balance of evidence suggests that oxygen does have symptomatic effects in COPD and also probably in congestive heart failure, patients with dyspnea due to cancer most frequently have restrictive respiratory failure that might not respond to oxygen in the same way. There are three randomized controlled trials in which cancer patients with dyspnea were randomized in a crossover design to 5 liters (68,69) or 4 liters per minute of oxygen (70). In the first two studies, all patients were hypoxemic on room air. In these patients, oxygen had a significant beneficial effect. In the third study, only 6 of 38 evaluable patients were hypoxemic; both oxygen and air were significantly superior to baseline (70). Swinburn et al. (61) studied the role of oxygen in a group of 10 patients with interstitial lung disease in addition to their main sample of 12 patients with COPD. Results in interstitial lung disease patients were as beneficial as those observed in the COPD group.

Oxygen has been found to improve functional capacity in patients with COPD (71,72). It is possible that oxygen supplementation could improve function in patients with cancer dyspnea but such studies have not been conducted. The main objective of oxygen therapy in advanced cancer patients is symptomatic relief rather than the prevention of long-term complications; therefore, intermittent use can be acceptable and less psychologically burdensome in patients who present with intermittent exacerbations of dyspnea.

In summary, although more research is needed, there is some compelling evidence for the use of oxygen as a symptomatic treatment for patients with cancer-related dyspnea. In particular, patients who are hypoxemic on room air are quite likely to benefit from this approach. It is possible that oxygen would be effective in relieving dyspnea at concentrations higher than those required to maintain optimal saturation of hemoglobin. Anecdotal experience in cancer patients and patients with congestive heart failure suggest that oxygen might give significant symptom relief to patients who are not hypoxemic. This hypothesis should be tested in prospective clinical trials.

When there are doubts about the effectiveness of oxygen for symptom relief in a given patient, an “N of 1” study can be conducted (69). The method used by the investigators in this study is summarized in Table 25-2. By performing multiple, double-blind crossovers between oxygen and air, it is possible to determine with great accuracy, in less than 1 hour, whether a specific patient does or does not benefit from the supplemental oxygen.

Measurements
O_2 saturation—pulse oximetry
Visual analogue scale scores of dyspnea: baseline and during blinded treatment with oxygen and air
Patient and investigator selected treatment of choice
Patient rated differences between the two treatments
Procedure
1. Baseline 5 min—no treatment
2. Patient and investigator blinded to treatments, either 5 l/min of 100% oxygen or air via face mask for 5 min
3. Followed directly by 5 min of alternate treatment
4. Repeat steps 1–3 six times

TABLE 25-2. N OF 1 STUDY FOR ASSESSMENT OF EFFECT OF SUPPLEMENTAL OXYGEN ON DYSPNEA

Pharmacological Interventions

A number of drugs have been suggested to affect the intensity of dyspnea in patients with cancer and other chronic conditions.

Opioids

Table 25-3 summarizes studies on the use of opioids in the treatment of dyspnea associated with a number of nonmalignant conditions (74,75,76,77,78,79,80 and 81). Table 25-4 summarizes studies of systemic opioids in the treatment of cancer-related dyspnea. In the case of cancer-related dyspnea, all the published studies have agreed on the beneficial effect of systemic opioids for cancer dyspnea (82,83,84,85,86 and 87). However, the optimal type, dose, and modality of administration of opioids has not yet been determined. Cohen et al. (84) treated eight patients with cancer dyspnea with continuous intravenous morphine. Significant symptomatic relief was observed, but the authors found that in this population of patients with no previous exposure to morphine, the continuous intravenous infusion resulted in a significant increase in the levels of PCO_2 . Bruera et al. (82,83) conducted two trials using intermittent subcutaneous morphine for the relief of cancer dyspnea. In the second study (83), intermittent doses of up to 2.5 times the regular opioid dose resulted in no significant change in the end-tidal CO_2 level. Most of these patients had already been chronically exposed to opioids and therefore had developed tolerance to their respiratory depressant effects. Mazzocato et al. (86), in a double-blind, crossover trial, looked at the effect of morphine 5 mg in seven opioid-naïve elderly cancer patients and 3.5 mg in addition to their regular dose in two patients already on 7.5 mg oral morphine every 4 hours. They found a significant improvement in dyspnea following treatment with morphine as compared with placebo with no significant changes in oxygen saturation.

Author (reference)	No. of patients	Opioid	Disease	Study	Level of evidence[a]	Effect on dyspnea	Assessment
Poole et al. (75)	18	Sustained release morphine (20 mg twice daily) or placebo	COPD	4 wk	I	+	CRQ, VAS case-control scale
Browning et al. (76)	7	Hydrocodone (oral 20 mg/4 hr) or placebo	COPD	Acute	I	+	VAS
Woodcock et al. (77)	12	Dihydrocodeine (1 mg/kg oral)	COPD	Acute	I	+	VAS
Johnson et al. (78)	18	Dihydrocodeine (15 mg three times/d) or placebo	COPD	3 wk	I	+	VAS
Rajagopal and Bruera (79)	1	Hydromorphone suppositories (3 mg 3–4 times/d)	COPD	Acute	I (N of 1)	+	Categorical scale
Eiser et al. (80)	4	Diamorphine (oral 2.5, 5.0, or 7.5 mg 4 hourly) or placebo	COPD	2 wk	I	-	VAS
Rice et al. (81)	11	Codeine (30 mg 4 times/d) or promethazine (25 mg 4 times/d)	COPD	1 mo	I	+	VAS
Light et al. (84)	10	Morphine (oral 0.8 mg/kg) or placebo	COPD	Acute	I	+	Borg scale
Sastmer (87)	17,8	Hydrocodone (5 mg (oral))	COPD	Acute	III	+	Not reported

COPD, chronic obstructive pulmonary disease; CRQ, chronic respiratory questionnaire; VAS, visual analogue scale; +, effective; -, not effective.
[a]Medline search from 1966–2000 of studies on the symptomatic treatment of dyspnea.
[a]Level of evidence: I, randomized controlled trial; III, retrospective study.

TABLE 25-3. USE OF OPIOIDS IN DYSPNEA ASSOCIATED WITH NONMALIGNANT CONDITIONS[a]

Author (reference)	No. of patients	Opioid drug	Disease	Study	Level of evidence[a]	Assessment	Findings
Bruera et al. (82)	10	Morphine s.c., 50% higher than regular scheduled dose	Advanced cancer	Acute	I	VAS	+
Mazzocato et al. (86)	9	Morphine s.c., 5 mg if opioid naïve or ½ daily oral dose	Advanced cancer	Acute	I	VAS and Borg scale	+
Allard et al. (87)	33	Morphine 25% or 50% of 4 hourly opioid dose by same route	Advanced cancer	Acute	I	VAS	+/-
Bruera et al. (83)	20	Morphine s.c., 5 mg bolus or 2.5 times the regular dose	Advanced cancer	Acute	III	VAS	+
Cohen et al. (84)	8	Morphine i.v. bolus, mean dose 5.6 mg/h	Advanced cancer	Acute	III	Categorical scale	+
Yamaguchi et al. (85)	5	Morphine s.c., 10 mg Chlorpromazine s.c., 25 mg	Advanced cancer	Acute	III	VAS	+

VAS, visual analogue scale; +, effective; +/-, very effective.
[a]Medline search from 1966–2000 of studies on the symptomatic treatment of dyspnea.
[a]Level of evidence, I, randomized controlled trial; III, retrospective study.

TABLE 25-4. SYSTEMIC OPIOIDS IN THE TREATMENT OF CANCER-RELATED DYSPNEA[a]

Allard et al. (87) looked at the effect of two different doses of opioids on dyspnea in patients receiving regular opioid therapy. Fifteen patient pairs were given supplemental doses of 25% or 50% of the equivalent 4-hourly dose. The findings suggested that 25% of the patient's usual 4-hourly dose was sufficient to reduce dyspnea intensity and tachypnea for 4 hours.

One of the main methodological problems in the design of clinical trials of opioids in cancer dyspnea is the changing intensity of dyspnea both spontaneously and as a result of definite maneuvers. For these reasons, some groups advocate the use of intermittent opioids, as needed, when dyspnea occurs or for the anticipation of dyspnea associated with specific maneuvers.

Nebulized Opioids

During recent years a number of authors reported symptomatic relief when patients with dyspnea are administered different types and doses of nebulized opioids (summarized in Table 25-5) (88,89,90,91 and 92). The possibility that opioids might affect receptors in the lung is exciting because of recent evidence suggesting that morphine does have an analgesic effect peripherally (93) and also because a small dose of nebulized morphine might be devoid of systemic opioid side effects.

Author (reference)	No. of patients	Drug	Disease	Level of evidence[a]	Findings	Assessment
Clark et al. (88)	78	Morphine (5–60 mg) or placebo	Cancer	I	-	VAS and modified Borg scale
Clark et al. (89)	18	Morphine (12.5 mg) or M-6-glucuronide (4 mg) or placebo	COPD	I	- + -	Objective measurement
Young et al. (90)	11	Morphine (5 mg/5 mL over 12 min) or placebo	COPD	I	+	Patient asked about limiting symptoms
Beaufort et al. (91)	8	Morphine (5, 4, or 10 mg) or placebo	COPD	I	-	VAS and objective measurement
Farncombe et al. (92)	54	34 pts morphine 1–20 mg/4 h	Cancer	III	34 patients + 12 stopped after 1 and 2 doses 8 conflicting reports on chart§	Not described
		17 pts hydromorphone 1–20 mg/4 h	COPD			
		2 pts codeine 15–60 mg/4 h				
		1 pt oxiviridine 25–50 mg/4 h				

COPD, chronic obstructive pulmonary disease; VAS, visual analogue scale; +, effective; -, not effective.
[a]Medline search from 1966–2000 of studies on the symptomatic treatment of dyspnea.
[b]Level of evidence: I, randomized controlled trial; III, retrospective study.

TABLE 25-5. USE OF NEBULIZED OPIOIDS IN DYSPNEA[a]

Pharmacokinetic studies suggest that the systemic bioavailability of nebulized morphine is extremely poor (94). Therefore, the effects reported in most studies would have to be of a local nature. This is further supported by the lack of reports of side effects usually observed when morphine is administered systemically, such as edation and nausea.

The evidence for a symptomatic effect in patients with COPD is controversial. Two controlled studies suggested a positive effect, in one case for morphine (90) and another case for morphine-6-glucuronide (89). Morphine was found to be ineffective in two studies (89,91). The largest uncontrolled study in cancer patients reported beneficial results (92). A more recent controlled trial in patients with cancer dyspnea showed no symptomatic benefit for nebulized morphine compared with placebo (88).

Benzodiazepines

Benzodiazepines are commonly used in the management of cancer-related dyspnea. Table 25-6 summarizes studies in which benzodiazepines were used for the management of dyspnea associated with both exercise and COPD (95,96,97,98 and 99). Four of the five studies found no significant difference between benzodiazepines and placebo. Mitchell-Heggs et al. (99) studied four patients with COPD in a controlled, single arm, blinded study comparing diazepam and placebo. The authors reported a sustained benefit for three of four patients after diazepam.

Author (ref.)	No. of patients	Psychotropic drug	Condition	Study	Level of evidence[a]	Effect of dyspnea
Stark et al. (95)	6	Diazepam (10 mg daily)	Exercise	Acute	I	-
		Promethazine (25 mg daily)				-
O'Neill et al. (96)	12	Promethazine (25 mg daily) and placebo	Exercise	Acute	I	-
	6	Methyrotolin (50 mg daily) or placebo (histamine antagonist)	Exercise			-
	6	Chlorpromazine (25 mg) or placebo				+
Woodcock et al. (97)	15	Diazepam (25 mg daily)	COPD	2 wk	I	-
		Promethazine (12.5 mg)				+
Wynn et al. (98)	24	Alprazolam (0.5 mg b.i.d.) or placebo	COPD	3 wk	I	-
Mitchell-Heggs et al. (99)	4	Diazepam (25 mg)	COPD	Acute	I	+

COPD, chronic obstructive pulmonary disease; +, effective; -, not effective.
[a]Medline search from 1966–2000 of studies on the symptomatic treatment of dyspnea.
[b]Level of evidence I, randomized controlled trial.

TABLE 25-6. EFFECT OF BENZODIAZEPINES ON DYSPNEA[a]

In some patients, benzodiazepines may be used when dyspnea is considered to be a somatic manifestation of a panic disorder or when patients have severe anxiety. There is no evidence to support the routine use of benzodiazepines in the management of dyspnea.

Corticosteroids

A number of authors have suggested that corticosteroids are highly effective in the management of dyspnea associated with carcinomatous lymphangitis. However, we are not aware of randomized controlled trials testing their role in this condition. In addition, corticosteroids are used frequently in the management of superior vena cava syndrome. They are highly effective in treating bronchospasm associated with both asthma and COPD (100,101). On the other hand, evidence exists that corticosteroids induce negative functional and pathological alterations in several muscle groups (102). It has been suggested that the effects are more pronounced on the diaphragm than on other muscles. These findings might be important because of the frequent presence of cachexia and muscle weakness in patients with advanced cancer.

Bronchodilators

Both nebulized and orally administered bronchodilators are useful in the management of bronchospasm associated with both asthma and COPD (100). A large proportion of the patients with cancer-related dyspnea have a history of smoking or COPD. Congleton and Muers (54) demonstrated that almost half of 57 consecutive patients with lung cancer treated by their group had evidence of airflow obstruction. A strong association was found between airflow obstruction and dyspnea. Of the 17 patients who accepted the offer of a trial of bronchodilator therapy (a combination of nebulized adrenergic and anticholinergic agents four times a day), most experienced significant symptomatic improvement.

Nebulized furosemide has been found to be protective against the bronchospasm induced by exercise in asthmatic patients (103). It has also been shown to have bronchodilator effect in acute asthma (104,105). There are reports of its use for the treatment of dyspnea in a palliative care setting (106).

Previous studies suggested that dyspnea in some patients with nonreversible obstructive airway disease could improve following the administration of theophylline (107). Aminophylline, theophylline, and caffeine all improve diaphragmatic contractility both in normal volunteers (107,108 and 109) and in patients with COPD (110). Because of the frequent presence of asthenia and generalized muscle weakness with or without cachexia (27), some cancer patients might benefit from the effect of xanthines on respiratory muscle contractility.

Other Drugs

Several studies suggested that alcohol might be able to decrease the intensity of dyspnea in patients with COPD (75,111). Although there is some consistent evidence for a symptomatic benefit for alcohol, the side effects associated with both acute and chronic administration, in addition to the potentially dangerous interaction with other drugs, suggests that alcohol may be an impractical option. A number of drugs, such as indomethacin (111) and medroxyprogesterone acetate (112), are being studied as a potential treatment for dyspnea, but the evidence for a role of these and other agents is very limited, and they could not be recommended for clinical use.

General Support Measures

A number of measures can be implemented for the support of the patient and the family. Most of these measures can be implemented in the acute-care hospital setting, continuingcare hospitals, and at home.

Activity Level

Dyspnea is a variable symptom. Most of the aggravating factors are related to muscle effort associated with different physical activities. It is important to educate patients and families so that they can recognize the type of maneuvers associated with episodes of increased dyspnea. Once these maneuvers are recognized, the two most effective approaches are anticipatory symptom relief and avoidance of effort. Anticipatory relief can include the administration of doses of drugs for symptomatic

relief before the dyspnea-causing maneuver, and psychological support techniques such as relaxation or imagery. Avoidance of effort involves assisting the patient to the maximum with the maneuver to minimize the muscle effort and the consequent development of dyspnea. This includes the use of different devices to assist the patient with transportation to and from the bathroom and for mobilization. It is important for patients and families to understand that they can remain quite active while not necessarily making muscle efforts. With the use of wheelchairs and portable oxygen it is possible for patients to return to the community.

On the other hand, there is substantial recent evidence that exercise programs and pulmonary rehabilitation in patients with COPD improve dyspnea and exercise tolerance (113,114,115,116,117 and 118). It is postulated that skeletal muscle dysfunction is an important contributor to exercise intolerance and dyspnea in COPD patients (117). The dysfunction is probably related to several factors, many of which also exist in advanced cancer patients, such as deconditioning secondary to immobility, malnutrition, and the use of corticosteroids. In addition inflammatory factors, such as interleukins and tumor necrosis factor, contribute to muscle wasting associated with cachexia in cancer patients.

Ventilatory Support

In patients with severe neuromuscular disorders, positive pressure ventilation provides significant relief for respiratory muscle fatigue. Techniques include continuous positive airway pressure ventilation or intermittent positive pressure ventilation via face or nasal masks. Continuous positive airway pressure ventilation has been shown to reduce inspiratory muscle effort and improve sleep in patients with both COPD and congestive heart failure, and to reduce dyspnea and fatigue in the latter group (119,120). By providing respiratory muscle relief, these techniques can decrease the sensation of breathlessness at rest and during exercise. The recognition of progressive muscle weakness in cancer patients and the correlation between maximal inspiratory pressure and dyspnea (14) indicate that some patients in whom respiratory muscle weakness can be demonstrated could possibly benefit from positive pressure ventilation. Specialized personnel, such as a chest physician or a trained chest therapist in an inpatient setting, should initiate these techniques.

Support of the Patient and Family

Explanation of dyspnea and addressing the fears of the patient and family is of great importance. Dyspnea can elicit major psychological reactions in the patient and the family, both of whom may fear that the patient may “choke to death.” It is important to anticipate the possibility of a crisis of respiratory failure. Symptomatic drugs should be made available together with instructions for administration. Telephone numbers of persons to be contacted should also be made available. Even if patients are not requiring oxygen at a given time, it is important that oxygen be available immediately if a respiratory crisis occurs.

Because dyspnea is frequently associated with tachypnea and the use of accessory respiratory muscles, patients may appear to be significantly dyspneic even when they are in good symptom control. As mentioned previously it is important for the relatives and members of the staff to remember to assess dyspnea only by asking patients how short of breath they feel rather than by estimating their dyspnea from the degree of tachypnea and use of accessory muscles. The goal should be symptomatic therapeutic intervention of the patient's expression of dyspnea rather than relief of the objective variables that accompany this symptom.

Future Research

Many aspects of dyspnea in cancer patients have not been adequately researched. These include areas of assessment and management. The use of simple noninvasive assessment methods, including reading and breath-holding, should be researched in greater detail. The potential role of descriptors of dyspnea to indicate underlying clinical conditions causing dyspnea should receive closer attention. Areas of treatment, including the roles of nebulized loop diuretics and various opioids, in addition to the effects of xanthines on respiratory muscle contractility, should be addressed by investigators. The effects of exercise training on dyspnea in patients with advanced cancer and the role of positive pressure ventilation in those with demonstrated respiratory muscle weakness should also be investigated.

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26

HEMOPTYSIS

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Hemoptysis, the coughing or expectoration of blood that originates in the lung, can be an alarming symptom for both patient and physician. It can range from bloodtinged or streaked sputum to *massive hemoptysis*, the latter defined as blood loss of 400–600 ml per day. Massive hemoptysis occurs in fewer than 5% of cases but carries a mortality rate of up to 85% if surgical intervention is not feasible (1,2). The management of hemoptysis, therefore, requires careful consideration of the cause, severity of the process, and functional status of the patient. Management may be more aggressive and invasive early in the course of a malignancy, whereas this could be inappropriate or dangerous for a patient in the terminal stages of an illness.

PATHOGENESIS

The lung is perfused by two distinct circulations that must be considered when determining the source and planned treatment of hemoptysis. The pulmonary circulation delivers blood under low pressure from the right ventricle to the alveolar capillaries for exchange of oxygen and carbon dioxide. The bronchial circulation, which is approximately 1–2% of the cardiac output, arises from the systemic circulation and provides nutrient flow to the lung parenchyma. A detailed review of the anatomy and physiology of the bronchial circulation has been published (3) and is beyond the scope of this chapter. In brief, two or more arteries arise from the aorta or upper intercostal arteries, enter the lung, and eventually form a plexus, which accompanies the branching airways with small, penetrating arteries, forming another plexus that supplies the bronchial mucosa down to the terminal bronchioles. Farther on, they anastomose with both precapillary pulmonary arterioles and pulmonary veins. Bronchial venous return is more complex: Veins from the proximal airways return blood to the right atrium via the azygos, hemiazygos, or intercostal veins, whereas the intrapulmonary bronchial venous blood returns via the pulmonary veins to the left ventricle. The latter occurs as a result of anastomoses between bronchial and pulmonary veins and carries the bulk of bronchial venous return. Although the bronchial circulation is nonessential in the normal adult lung, in the setting of chronic inflammation, neoplasm, or repair after lung injury, bronchial blood flow increases as the result of increases in both the size and number of vessels. Elevations of pulmonary vascular pressure can affect the bronchial circulation because of the many anastomoses between the dual circulations. In general, hemoptysis occurs because of disruption of the highpressure bronchial vessels, which become abnormally enlarged and exposed within diseased airways.

ETIOLOGY

This discussion concentrates on the malignant causes of hemoptysis, but awareness of other causes is important because many patients have underlying conditions that may become active problems during treatment of a malignant disease. The differential diagnosis for a patient presenting with hemoptysis is extensive (Table 26-1). Some conditions that are more likely to be associated with massive hemoptysis are shown in Table 26-2. In past years, tuberculosis, bronchiectasis, and lung abscess were the most common causes of massive hemoptysis. The incidence of the latter two has declined in industrialized nations, but tuberculosis remains a significant problem worldwide. Experience with tuberculosis has helped us to understand the pathophysiology of massive hemoptysis. Up to 7% of deaths from tuberculosis have been attributed to massive hemoptysis; autopsy examinations have revealed ruptured pulmonary artery aneurysms. Rasmussen (4) described localized ruptures of aneurysmal portions of pulmonary arteries passing through thick-walled cavities of chronic tuberculosis, so-called “Rasmussen's aneurysms.” Rupture occurs secondary to the infection or the associated inflammatory response (4). Healed calcified mediastinal lymph nodes from prior tuberculosis can erode into the bronchial mucosa, also causing significant bleeding. Tuberculosis distorts lung architecture, causing bronchiectasis with resulting hypertrophy and proliferation of bronchial vessels. Infection or inflammation in these diseased portions of airway can cause rupture of vessels; the result is massive bleeding caused by the high systemic arterial pressure.

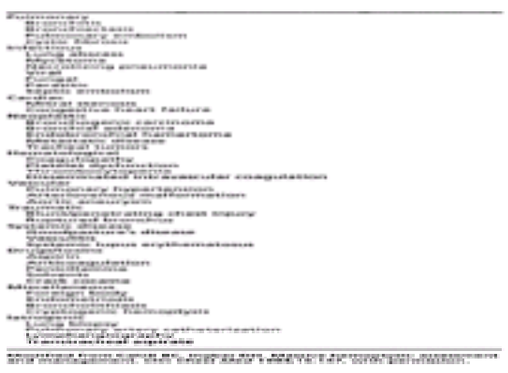

TABLE 26-1. CAUSES OF HEMOPTYSIS

Pulmonary tuberculosis
Bronchiectasis
Lung abscess
Mycetoma
Bronchogenic carcinoma
Pulmonary carcinoid
Pulmonary arteriovenous fistula
Pulmonary vasculitis
Broncholithiasis

TABLE 26-2. CAUSES OF MASSIVE HEMOPTYSIS

Nonmalignant Conditions

Patients with preexisting cavitary lung disease resulting from mycobacterial infections, sarcoidosis, bullous emphysema, lung abscess, lung infarction, and fibrocavitary disease secondary to rheumatoid disease are at risk for mycetoma formation, most often due to *Aspergillus*. This noninvasive infection results in a thick-walled cavity with vascular granulation tissue and inflammatory cells, the former the result of proliferation of the bronchial circulation. Bleeding is a result of vascular injury from

fungal endotoxin, proteolytic activity, or a type III hypersensitivity reaction (5). Bacterial superinfection also can promote hemoptysis in the setting.

Deep venous thrombosis and subsequent thromboembolic disease are common in hospitalized patients, especially those with underlying risk factors. The presence of a malignancy is a major risk factor, and the onset of hemoptysis warrants consideration of the possibility of pulmonary embolism and subsequent infarction. With current standard anticoagulation therapy, pulmonary embolism is a treatable condition with a 2.5% mortality rate. In a prospective study of the clinical course of pulmonary embolism, almost 24% of patients died within 1 year of diagnosis. Many cases, approximately 35%, had some form of cancer (6). A less well-appreciated and studied source of pulmonary embolism is upper extremity thrombosis resulting from indwelling venous catheters. In some series, the incidence of central line thromboembolism has been as high as 12% (7). Although most commonly seen in the pediatric population, there have been reports of inhaled foreign bodies in adults that, if unrecognized, have caused hemoptysis (8).

Malignant Conditions

In a retrospective review of 877 cases of lung cancer, Miller and McGregor (9) reported a 19.3% overall incidence of hemoptysis, with non–life-threatening hemoptysis occurring equally among histologic types (9). Twentynine cases (3.3%) were massive and terminal events, due almost exclusively to proximal, cavitary squamous cell carcinomas. In only 6 of these 29 cases was there no antecedent nonlethal bleeding. The cause of this sudden catastrophic bleeding was tumor hemorrhage or invasion of a pulmonary artery or vein. In another series, Panos et al. (10) also found an association between cavitary squamous cell tumors and fatal hemoptysis. Metastatic endobronchial disease (carcinoma of breast, colon, kidney, and melanoma) is more likely to cause nonfatal hemoptysis rather than a terminal bleeding event. The incidence of hemoptysis in patients with bronchial carcinoid tumors approaches 50%, resulting from mucosal ulceration or airway inflammation disrupting the bronchial arteries supplying these tumors. The high incidence of symptomatic bleeding is not surprising, as 85% of carcinoids arise in the proximal airway and are often very vascular (11). Malignant tracheal tumors are uncommon; when present, they usually result in obstructive symptoms. Hemoptysis does occur from these tumors, but less frequently than with bronchogenic carcinoma (12). A Danish series of pulmonary hamartoma cases found that only 39% of patients were symptomatic but that nearly onefourth of those patients noted hemoptysis (13).

Patients with a hematological malignancy may develop hemoptysis for many reasons, including thrombocytopenia, coagulation abnormalities, and infections. In one series, fatal hemoptysis was associated strongly with the autopsy findings of vascular invasion, thrombosis, and hemorrhagic infarction secondary to invasive fungal disease (14). Idiopathic alveolar hemorrhage is a rare cause of fatal hemoptysis, accounting for only 2–3% of leukemia deaths, but it also is associated with nonfatal hemoptysis. This is hypothesized to be attributable to the combination of thrombocytopenia and diffuse alveolar damage, the latter a result of chemotherapy, radiotherapy, sepsis, viral infection, or a combination of any of these (14).

Thromboembolic disease already has been discussed in this chapter, but pulmonary embolic disease also may be caused by intravascular tumor metastases, resulting in a clinical presentation indistinguishable from the more common venous thromboembolism. Hemoptysis is unusual, and symptoms of dyspnea and right heart failure predominate. Rarely, massive tumor embolism results in pulmonary infarction with hemoptysis. Pulmonary infarction due to malignant compression of pulmonary veins also has been reported (15).

DIAGNOSIS

The key element of diagnosis in cases of hemoptysis is the localization of bleeding to the lower respiratory tract. Although blood from the stomach usually has a low pH and blood from the respiratory tract a high pH, bleeding from the nasopharynx, larynx, or gastrointestinal tract may be difficult to distinguish clinically from hemoptysis. Furthermore, bleeding from these sources may result in cough and the appearance of blood, which can be misinterpreted as hemoptysis. When there is doubt, a thorough examination of the nasopharynx, larynx, and upper gastrointestinal tract should be performed.

Once the lung has been identified as the source of bleeding, the next step is to localize the site of bleeding. Physical examination alone is not sensitive enough; a chest radiograph should be performed, and often is helpful in revealing a tumor or abscess. However, it can be misleading, as blood may be coughed into uninvolved portions of the lungs. Bronchoscopy is the surest way to visualize the source (or at least the segment) from which there is active bleeding. Flexible fiberoptic bronchoscopy usually is attempted first because it can be done relatively quickly at the bedside without putting the patient under general anesthesia and can access more distal airways than the rigid bronchoscope. The latter has the advantages of greater suction capability, removal of clots or foreign bodies, and airway control that allows for patient ventilation, often necessary in cases of massive hemoptysis. Computed tomography (CT) scan has been compared with bronchoscopy in studies in which hemoptysis is the presenting problem. Patients with preexisting cancer constituted a small proportion of those studied. A CT scan is superior in identifying bronchiectasis, lung abscess, aspergilloma, and distal parenchymal abnormalities; however, the bronchoscope can obtain material that allows a cytological, histological, and microbiological diagnosis (16,17). In patients with established malignancies, a CT scan may offer important information, as it can delineate peribronchial or mediastinal involvement of tumors that cannot be seen with a bronchoscope. Routine use of CT is not of proven benefit but should be considered in cases in which the chest radiographic findings are inconclusive or to provide a more detailed anatomical localization of an abnormality for the bronchoscopist.

MANAGEMENT

The severity of hemoptysis determines the pace at which a work up should proceed. In a review of 10 years' experience at Duke University Medical Center, the mortality rate was 9% and 58% if blood loss was less than or more than 1000 ml per 24-hour period, respectively (1). A malignant cause for hemoptysis of greater than 1000 ml per 24 hours increased the mortality rate to 80%. Massive hemoptysis requires rapid intervention to guarantee that the patient has an adequate airway while attempting to control bleeding. If blood loss is minimal and sporadic, a more detailed evaluation can occur without immediate attention to resuscitative efforts. Early consultation with a pulmonary physician and thoracic surgeon is recommended.

Initial diagnostic studies should include chest radiograph, hematocrit, platelet count, blood urea nitrogen and creatinine levels, and coagulation panel, which might include a bleeding time if aspirin or nonsteroidal antiinflammatory agents have recently been used. Oxygenation should be monitored by arterial blood gas determination or pulse oximetry and adequate intravenous access established. Typed and crossmatched blood should be available in cases. of significant bleeding. Mild sedation and judicious use of a cough suppressant can be employed, but excessive use compromises a patient's ability to clear their airway.

If oxygenation is compromised or the patient continues to bleed vigorously, elective intubation should be considered. The endotracheal tube should be large enough to allow passage of a bronchoscope (7.5 or 8.0 mm). If it is known from which side the patient is bleeding, the patient should be placed in a lateral decubitus position with the bleeding side down to help minimize aspiration of blood into the good lung. Placement of a doublelumen endotracheal tube is sometimes necessary to allow separate ventilation of each lung while preventing aspiration of blood throughout the bronchial tree. The two small lumina preclude bronchoscopy with anything but a pediatric bronchoscope, and suctioning is limited because only small-caliber catheters can be passed distally. Newer-generation tubes with larger internal diameters may be less troublesome (18). The decision to intubate a patient with a terminal illness may be difficult. If bleeding can be localized and controlled quickly, a short period of intubation may not be unreasonable if it allows for improved quality of life. This would be unlikely for a patient in the later stages of a terminal illness, especially in the setting of massive hemoptysis.

Bronchoscopy

If bronchoscopy identifies the site of bleeding, several maneuvers can be done to stop or slow the bleeding. Bronchial lavage with iced saline (19), application of topical epinephrine (1:20,000), and topical thrombin and fibrinogen-thrombin solutions (20) all have been reported in small series to have varied success; however, they have not been evaluated in large numbers of patients in controlled studies. A pulmonary tamponade balloon can be inflated in the segmental bronchus leading to the site of bleeding, allowing time for stabilization of the patient and consideration of more definitive therapy 21). Bleeding from visible lesions in the trachea and proximal bronchi can be coagulated with a laser. This is particularly useful when the hemoptysis arises from an obstructing tumor, as both problems can be addressed simultaneously. In a series of 43 patients with advanced bronchogenic carcinoma (16 with concomitant hemoptysis), 38 were treated successfully (22). One patient died of continued tumor bleeding and aspiration of blood and two required tracheostomy to facilitate management of secretions. There was one pneumothorax, and one transient bronchial obstruction by a tumor fragment mobilized by laser therapy.

Radiotherapy

External beam radiation for 6–7 weeks usually is employed to attempt cure for inoperable nonsmall cell carcinoma. In the palliative setting, therapy is delivered in the shortest time possible, with lower doses to achieve symptom relief while minimizing side effects: 8 Gy in 1 fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions have all been used with success. Hemoptysis can be stopped in more than 80% of cases by using palliative radiotherapy (23). Although significant symptoms from radiation fibrosis are uncommon, there are reports of massive hemoptysis occurring long after, and attributed to, external beam radiotherapy (24). Such cases are rare, however, probably because most patients succumb to their underlying cancer before significant vascular abnormalities develop.

Endobronchial brachytherapy with iridium 192 is another alternative. A useful summary of this modality is available (25). Dose rates can be low (up to 1 Gy per hour), intermediate (2–10 Gy per hour), or high (greater than 10 Gy per hour). The higher dose rates decrease the time of treatment and permit outpatient rather than

inpatient therapy. Gollins et al. (26) reported results of high-dose-rate brachytherapy in 406 patients. Of 255 patients with hemoptysis, brachytherapy arrested the bleeding in 89% at 1.5 months, 84% at 4 months, and 77% at 12 months after the first treatment. The results were not as favorable for patients who received brachytherapy after failure of external beam radiation; 84%, 56%, and 25% of patients had resolution of hemoptysis 1.5, 4, and 12 months after brachytherapy, respectively. Although most patients died of their cancer during the study (mean survival was 173 days), control of hemoptysis was quite good. Massive hemoptysis as a terminal event occurred in 32 patients (8%). Retrospective results of different brachytherapy dose rates are summarized in Table 26-3. Brachytherapy has been combined with bronchoscopic laser therapy in some centers (27,28). The Mayo Clinic reported results from 65 patients, 40 of whom had received prior laser therapy. In 24 patients with hemoptysis, bleeding resolved in 19. Response was poorer in patients who had received laser therapy, most likely because of more advanced disease (28). Potential complications of brachytherapy include mucositis, fistula formation, and fatal hemoptysis (29). The latter event has a reported incidence of 6–30%. Recent studies have addressed the issue of hemoptysis in more detail. Hennequin et al. (30) documented a 7.4% rate of hemoptysis after intermediate dose rates given to149 patients. Multivariate analysis indicated that tumor length and upper lobe location were risk factors for hemoptysis. In this series, 10 of 11 cases of hemoptysis were fatal; and all but one case occurred in patients with progressive disease. Other studies have implicated highdose-rate brachytherapy (³15 Gy) as a risk factor for fatal hemoptysis, particularly in patients who have already received external beam radiation (31,32).

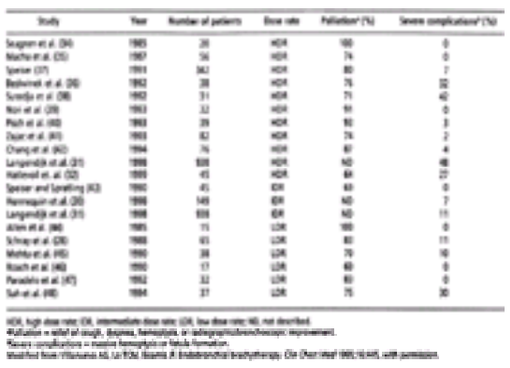

TABLE 26-3. ENDOBRONCHIAL BRACHYTHERAPY

Bronchial Artery Embolization

Bronchial artery anatomy is quite variable but generally arises from the ventral surface of the descending aorta or as branches from the intercostal arteries at the level of T5 and T6. Intimate knowledge of this vascular anatomy is essential because the anterior spinal artery often arises from the bronchial arteries and inadvertent embolization could result in spinal cord infarction. Bronchiectasis, tuberculosis, and aspergilloma frequently result in hypertrophy of bronchial vessels, but there are often transpleural collaterals from other systemic vessels, such as the subclavian, internal mammary, or intercostal arteries, which must be identified. After angiographic identification of the vessels in question, a variety of agents (e.g., Gelfoam, polyvinyl alcohol particles, and metallic coils) can be injected selectively to stop blood flow. Initial success rates reported in the literature vary between 75% and 90%, with a rebleeding rate of 15–30%. Hayakawa and colleagues (33) reported immediate (within 1 month) and long-term results for 63 patients. Of the 12 patients with hemoptysis due to neoplasm, bleeding was controlled in seven (58%). Long-term control was documented for four of these seven patients, with a median hemoptysis control period of 6 months (range, 0–9 months). All but one of the patients died within the 9-month followup period. Patients with bronchiectasis, inflammation, or idiopathic causes had immediate control in 94% of cases, with the median period of control lasting 15 months (range, 1–132 months) and a mortality rate of 11%. Recurrent bleeding can be treated with repeat embolization.

Surgery

The definitive therapy for massive hemoptysis is resection of the diseased portion of the lung; however, this is often precluded by the severity of the underlying lung disease. Similarly, massive hemoptysis from a bronchogenic carcinoma usually results from proximal endobronchial tumor, which is typically not amenable to surgical resection. Therefore, surgery is not an option for the vast majority of palliative care patients.

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27

AIRWAY OBSTRUCTION, BRONCHOSPASM, AND COUGH

JULIE A. BILLER

Disorders of the airways may produce debilitating or life-threatening symptoms in a diverse patient population. Therefore, health care providers, including generalists and those of many subspecialties, may be called on to diagnose and treat these disorders. Often, a multidisciplinary approach is needed. Airway obstruction, bronchospasm, stridor, and cough not only may produce symptoms that reduce the quality of life of the patients affected, but they can produce profound distress to those patients' families. In some situations, even our current best therapies do little to palliate symptoms. It is my hope that we shall see continued improvement in these areas. In this chapter, the diagnostic and current therapeutic approach to airway disorders are reviewed.

TRACHEOBRONCHIAL OBSTRUCTION

The tracheobronchial tree quite literally can be “between a rock and a hard place,” resulting in airway obstruction. Obstruction may occur on the basis of large exophytic endobronchial tumor causing intrinsic obstruction of the airway. On the other hand, mediastinal pathology can cause obstruction by extrinsic compression of the airways. Etiologies differ somewhat between the two modes of obstruction. *Intrinsic* obstruction usually is caused by primary malignancies arising from the airway epithelium. Two histologic types of tumors, squamous cell carcinoma and adenoid cystic carcinoma, constitute twothirds of the primary tracheal malignancies (1). The remaining third comprises a diverse group of tumors, both benign and malignant, detailed in Table 27-1. More commonly, the trachea can be a site of locally extensive disease, usually from organs in close proximity, such as the lung, larynx, thyroid, and esophagus. Intrinsic obstruction of the bronchial tree most frequently is seen in primary cancers of all histologic types. Approximately 5% of metastatic disease to the lungs is predominately endobronchial. Renal cell, colon, rectum, cervical, breast carcinomas, and malignant melanomas are the most common primary malignancies to give rise to endobronchial metastasis (2).

Intrinsic obstruction	Chondromas
Malignant	Hamartoma
Primary tumors	Lipoma
Tracheal	Leiomyoma
Squamous carcinoma	Granular cell myoblastoma
Adenoid cystic carci-noma	Granuloma 2 retained for-eign body
Bronchogenic	Hemangiomas
Squamous	Postintubation strictures
Adenocarcinoma	Low-grade malignancy
Small cell	Carcinoid
Mixed morphology	Extrinsic obstruction
Metastatic	Malignancy
Breast cancer	Lung
Melanoma	Lymphoma
Larynx	Esophageal
Esophagus	Thyroid
Renal cell	Benign
Colon	Fungal infection
Rectal	Reactive lymphadenopathy
Cervical	Bronchomalacia
Kaposi sarcoma (rarely obstructing)	Mediastinal fibrosis
Benign	Vascular compression
Papillomas	Goiter

TABLE 27-1. ETIOLOGIES OF AIRWAY OBSTRUCTION

Extrinsic obstruction occurs when the airways are surrounded by firm tumor or encased by pathologically enlarged lymph nodes, usually caused by locally advanced disease arising from the lung, esophagus, and thyroid. Lymphoma, which can involve significant lymphadenopathy, is another cause of extrinsic compression. A variety of benign lesions that may imperil airway patency are listed in Table 27-1.

Evaluation

Patients with tracheobronchial obstruction usually present with complaints of dyspnea, hemoptysis, wheezing, or stridor, and sometimes with pneumonia or atelectasis. The onset of these obstructive symptoms can be insidious, and patients often are treated for other diseases, such as asthma or chronic obstructive pulmonary disease (COPD). Patients occasionally come to medical attention when pulmonary function tests obtained for other reasons suggest upper airway obstruction.

The evaluation of airway obstruction is primarily through radiographical studies and bronchoscopy. Posteroanterior and lateral chest radiographs should be the first diagnostic study ordered. Grossly abnormal radiographs with a large central parenchymal mass or mediastinal mass/adenopathy causing tracheal narrowing or deviation rapidly raise concern for the patency of the airway. Unfortunately, there can be significant compromise to the airway but only subtle radiographical changes. Therefore, close attention must be paid to the tracheal air column. Often, abnormalities are more obvious on the lateral view.

Computed tomography (CT) of the neck and chest are extremely useful for better definition of airway anatomy, allowing accurate measurement of the diameter of the central airways to determine the extent of obstruction. It is important in treatment planning to determine whether the obstruction is primarily intrinsic or extrinsic. This differentiation often can be made by CT scan. In medically stable patients, pulmonary function testing, including spirometry and, most important, flowvolume loop, may identify upper airway obstruction quickly, inexpensively, and noninvasively. Frequently, such testing can localize whether the obstruction is extrathoracic or intrathoracic. Figure 27-1A shows the typical flow-volume loop in a fixed airway obstruction. The most common causes of this type of lesion are tracheal stenosis, tumor (malignant or benign), goiter, fixation of vocal cords, and a large foreign body. Variable, extrathoracic, upper airway obstruction (Fig. 27-1B) affects primarily the inspiratory loop of the flow-volume curve. Common causes of this are bilateral vocal cord paralysis, epiglottis, vocal cord adhesions, and foreign body. Variable intrathoracic obstruction (Fig. 27-1C) affects primarily the expiratory loop of the flow-volume curve after the effortdependent peak expiratory flow, which can be caused by intraluminal polypoid tumors or tracheomalacia.

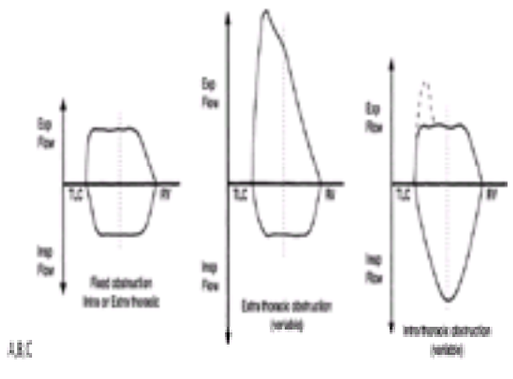

FIGURE 27-1. A: Maximal inspiratory and expiratory flow-volume curves in fixed obstruction. **B:** Extrathoracic variable obstruction. **C:** Intrathoracic variable obstruction. Dashed line represents a flow transient that occasionally is observed just before the plateau in intrathoracic obstruction. RV, residual volume;TLC, total lung capacity. (From Kryger et al. Diagnosis of obstruction of the upper and central airways.Am J Med 1976;61:85–93, with permission.)

To complete the evaluation of the patient with upper airway obstruction, more invasive procedures may be necessary, which typically involve fiberoptic evaluation, including laryngoscopy or bronchoscopy. It may be necessary to have multiple subspecialists involved in complicated cases, including otolaryngologists, thoracic surgeons, pulmonologists, and anesthesiologists. Bronchoscopy may be performed for several reasons, principally to obtain pathological material for diagnosis or as a therapeutic maneuver (see the section Therapy below). This is especially important if small cell lung carcinoma is considered in the differential diagnosis. If there is any question about the adequacy of the airway, bronchoscopy is best performed by a thoracic surgeon in the operating room with an experienced anesthesiologist present. At biopsy, the patient may have complications of airway obstruction or hemorrhage, which may endanger a marginal airway. Frequently, in this patient population, rigid bronchoscopy, with its better suctioning capabilities and ability to ventilate through the bronchoscope, is the procedure of choice.

Therapy

Patients who have airway obstruction on the basis of primary malignancies of the trachea or larynx, benign strictures (such as postintubation tracheal stenosis or extrinsic compression secondary to goiter or lymphoma) should be referred to the appropriate specialist (surgeon, oncologist, or radiation oncologist) for evaluation of definitive therapy Palliative therapeutic options for airway management in patients who are not candidates for definitive therapeutic procedures include airway stents, laser therapy, brachytherapy, and tracheostomy. Some patients may be helped by using several of these modalities in combination.

For any palliative therapy to be attempted, the airway must be wide enough to allow passage of a rigid or flexible bronchoscope and still maintain oxygenation and ventilation. In the case of large exophytic tumors that compromise the patency of the central airways, the bronchoscopist still can usually pass a bronchoscope instrument past the tumor. If this is not possible, a rigid bronchoscope may be used to “core out” the obstructing tumor, with its tip inserted in corkscrew fashion (1). If significant bleeding occurs, the rigid bronchoscope may be used to exert pressure and tamponade the bleeding. Ventilation can be maintained through the rigid bronchoscope, and it has a large suction channel to clear blood and tissue from the airways. Sometimes it is necessary to pass a fiberoptic bronchoscope through the rigid bronchoscope to clear blood, secretions, or tissue fragments from the more distal airways. Some authors are strong proponents of this technique. Although it requires expertise to reduce the risk of complications, such as tracheal perforation, hemorrhage, or rupture of the pulmonary artery, it does not need special equipment and usually requires only one endoscopic procedure. In a series from Mathisen and Grillo (3), 51 of 56 patients had significant improvement in airway obstruction after bronchoscopic “core out,” and only two patients required a second procedure. The patients who did not improve had distal obstructing disease. Because a rigid bronchoscope is used to perform a “core out,” it is best suited for large, central airway disease. Distal lesions or those obstructing the upper lobe orifices are less likely to be accessible with a rigid bronchoscope.

The other option for palliative resection of intrinsically obstructing lesions of the large airways is laser endobronchial resection (Fig. 27-2, Fig. 27-3) (3). Lasers transform light energy to heat, which causes tissue coagulation and vaporization. With advances in laser technology, this has become an increasingly popular modality over the past 15 years. Currently, the neodymium:yttrium, aluminum, garnet (Nd:YAG) laser is best suited for endobronchial resection. These lasers can be delivered through both rigid and flexible bronchoscopes. The wavelength of the laser is such that it is poorly absorbed by hemoglobin and water, resulting in deep tissue penetration. Because of high-power output, it can thermally coagulate blood vessels up to 2–3 mm in diameter and vaporize tissue (4). There seems to be a preference toward rigid bronchoscopy because of its ability to ventilate the patient better and its improved suctioning abilities. However, there are many reports of the use of flexible fiberoptic bronchoscopic resections in patients unable to tolerate general anesthesia and rigid bronchoscopy (5,6). In some situations, both types of procedures may be performed in combination. The bronchoscope is passed into the airway and the base of the tumor is identified. The Nd:YAG laser is aimed at the base of the tumor parallel to the wall of the trachea. Using varying energy levels, pulsations of laser energy are used first to coagulate the tumor mass and then to vaporize the tissue. The tracheal wall is avoided to reduce the risk of perforation or hemorrhage. In addition to these complications, there is also risk of tracheoesophageal fistula formation, combustion and fire within the bronchoscope, and ocular damage to operating personnel if appropriate protective gear is not used. Other drawbacks to laser resection include the need for special equipment and its time-consuming nature. Most patients improve after the first endoscopic resection but may require multiple sessions to complete the excision.

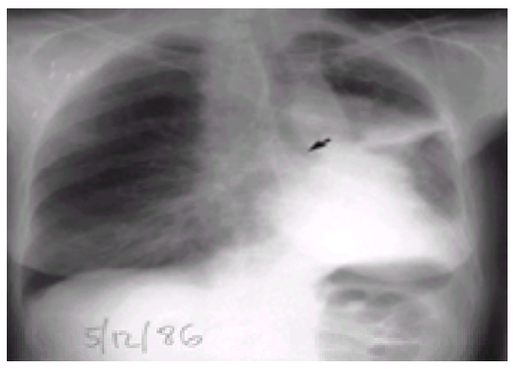

FIGURE 27-2. Chest radiograph showing cutoff airway (arrow) from obstructing tumor, significant volume loss of the left hemithorax, and postobstructive pneumonia.

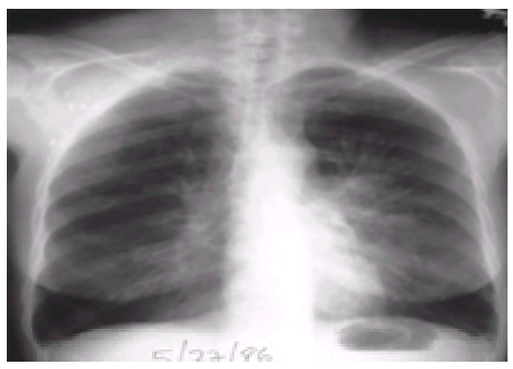

FIGURE 27-3. Chest radiograph of the same patient after laser resection of the tumor. Notice the resolution of volume loss and resolving pneumonitis.

Success rates are quite substantial with most patients having relief of symptoms or reexpansion of obstructed lung. In a series of 100 Nd:YAG-laser ablations performed on 40 patients, 22 patients were considered to have an excellent response to therapy and another ten a fair response (7). Besides improving quality of life, some patients have prolonged survival from what would otherwise have been a fatal complication of their underlying disease.

Bronchoscopic brachytherapy is the placement of a radiation source in close proximity to an endobronchial tumor. *Brachytherapy*, or short-distance therapy, is in contrast to conventional, external-beam radiation therapy delivered at a distance from the lesion. Brachytherapy is another modality to palliate locally extensive disease in the airways. Patients first undergo bronchoscopy to evaluate the extent of intraluminal tumor. A catheter then is advanced through a channel in the bronchoscope to the desired level, and the bronchoscope is removed. Correct placement is verified by reinsertion of the bronchoscope. The catheter is secured to the nasal orifice, and a radioactive source, usually iridium-192 or iodine-125, is placed in the catheter. Conventional-dose brachytherapy (50–120 cGy/hr) requires the catheter to remain inserted for 48–96 hours with the patient in a shielded hospital room. High-dose brachytherapy (675 cGy/min at 1 cm), delivered by a Gamnaed II remote afterloading unit, has a treatment duration of only a few minutes. No special radiation measures are needed for the patient after the afterloading unit is removed. Patients must have sufficient pulmonary reserve to undergo bronchoscopy and catheter placement. Brachytherapy also can be delivered by the insertion of radiation seeds or pellets into endobrachial lesions. Brachytherapy can improve symptoms of dyspnea and hemoptysis in approximately 90% of patients with stable airway disease (8). Because of

the need for a stable airway, several studies combined laser endobronchial resection with brachytherapy (4,9). High-dose brachytherapy was tolerated better with slightly improved survival compared with conventional-dose brachytherapy. Early complications to brachytherapy include airway obstruction secondary to mucous plugs requiring therapeutic bronchoscopy, radiation esophagitis, and laryngospasm. Long-term complications are more ominous, including fatal hemorrhage from fistula formation between airways and major blood vessels as well as airway esophageal fistula formation (9). Long-term survivors are at risk of airway stenosis at the site of laser or radiation therapy (9).

Extrinsic compression of the airway is not amenable to the above-mentioned therapies. Pressure from extraluminal tumor, vasculature, or luminal weakness can cause the airways to narrow or collapse. Intraluminal pressure is needed to counteract these external forces. Over the past two decades, insertion of airway stents to maintain airway patency has gained popularity as an effective palliative treatment for extrinsic compression. Stents can be inserted through rigid or flexible bronchoscopes. Their most impressive benefit is the immediate palliation of airway obstruction on placement of the stent (Fig. 27-4, Fig. 27-5). Several different types of airway stents are available, including silicone stents (Dumon, Montgomery T-tube, Hood) or expandable metallic stents (Gianturco, Wall, William Cook, etc.). Both types of stents are placed in a similar manner. The stents are compressed to an extremely small diameter within an introducer and are inserted into the airway bronchoscopically after the airway has been dilated with either a balloon or successively larger rigid bronchoscopes. When correct placement is verified, the stent is deployed, expanding to enlarge the airway. Stents come in varying diameters and lengths for use in the trachea and mainstem bronchi.

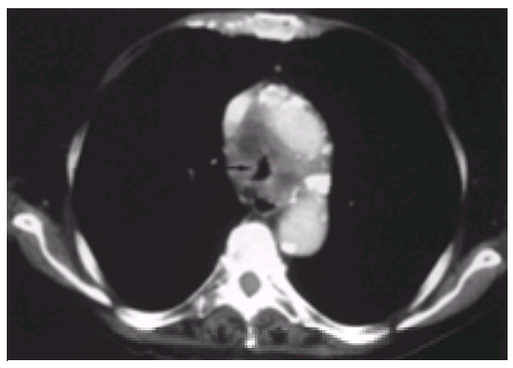

FIGURE 27-4. Tracheal compression (arrow) causing dyspnea in a 63-year-old woman. Biopsy of the tumor revealed squamous cell carcinoma.

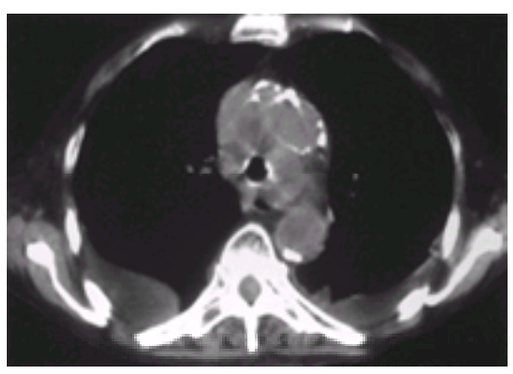

FIGURE 27-5. The same patient after placement of a stent into the trachea, which has increased the diameter of the airway and relieved her symptoms.

However, none of the stents is without drawbacks. Silicone stents may migrate or even may be coughed completely out of the airway. Therefore, it is extremely important to place the appropriately sized stent, as migration usually is seen with stents that are too small (10). Silicone stents placed in the right mainstem bronchus may obstruct the orifice to the right upper lobe, putting the patient at risk for atelectasis and infectious complications. Silicone stents also are believed to interfere with mucociliary clearance and pulmonary toilet (11). T-tube stents are placed in the trachea and usually require tracheostomy. A rare complication of stent placement is fatal erosion into a central vascular structure. Despite these potential drawbacks, silicone stents are well tolerated and quite successful in the treatment of extrinsic airway obstruction (12,13).

Expandable metallic stents are the newest type of stents to be used in the treatment of airway obstruction, but they have many drawbacks. Because these stents are made of loops of wire, they do not obstruct orifices of smaller airways, such as the opening of the right upper lobe, when placed in the right mainstem bronchus. Unfortunately, because of the loops, endobronchial tumor may grow through the stent and compromise the airway. The metallic stents have an irritant effect on the airways. Cough and granuloma formation are the most common complications (14). Some patients improve with inhaled corticosteroids and laser resection. Because of the tissue reaction, removal of the stents is difficult, often causing damage to the airways. There have been reports of fatal hemorrhage, broken suction catheters, stent migration, and stent breakage (15,16 and 17).

Last, some patients with upper airway obstruction may have relief of symptoms following tracheostomy, which is useful only in patients with laryngeal or very proximal tracheal obstruction. In patients with distal tracheal or small airway obstruction, the tracheostomy tube is not able to bypass the obstructing lesion. Recent improvements in tracheostomy tube technology can improve patient communication and decrease the risk of complications such as granulation tissue formation and bleeding.

Tracheobronchial obstruction is a devastating complication from both malignant and nonmalignant disease. There are many possible therapies for palliation. These therapies are not mutually exclusive, and their use in combination should be encouraged. A multidisciplinary approach with appropriately trained personnel is needed.

STRIDOR

Stridor is loud, harsh breathing, particularly on inspiration. It occurs from obstructed airflow in the upper airway and large intrathoracic central airways. Stridor may indicate a pathological narrowing of the airway, which is unable to maintain adequate oxygenation and ventilation of the patient. Therefore, evaluation and management of these patients should be done expediently. Treatment for stridor depends on the location of the obstruction and its etiology. When evaluating a patient presenting with stridor, it is useful to consider the airway as three areas or zones (18,19). The first is the *supraglottic zone*, which includes the nose, oral cavity, pharynx, and supraglottic larynx. This area is composed of soft tissues that are only loosely supported and hence more easily obstructed. Lesions in this area tend to cause stridor only on inspiration. The second is the *extrathoracic tracheal zone*, which is composed primarily of the glottis and subglottis. Because this area has more support, obstruction generally occurs more gradually. Lesions in this area may cause stridor both on inspiration and expiration known as *biphasic stridor*. Last is the *intrathoracic tracheal area*, which also includes the proximal portions of the mainstem bronchi. Stridor from this region may be primarily expiratory and may be confused with wheezing from distal intrathoracic airway obstruction. Of note, patients frequently deviate from these patterns of clinical presentations. The causes of stridor are numerous, some of which are listed in Table 27-2.

Infection
Tracheitis: bacterial or viral
Epiglottitis
Abscess: peritonsillar or retropharyngeal
Viral laryngotracheobronchitis
Neoplasm
See Table 27-1
Congenital
Laryngomalacia
Tracheomalacia/tracheal stenosis
Vocal cord cyst/paralysis
Webs
Trauma
Facial
Ingestion
Inhalation injury
Postintubation
Airway fracture
Postsurgical
Neurological
Central nervous system malformation
Hypoxic encephalopathy
Other
Foreign bodies (airway, esophageal)
Pyothogenic
Exercise

TABLE 27-2. CAUSES OF STRIDOR

Evaluation

The tempo of evaluation of the patient presenting with stridor is determined by the acuity of the illness. Patients who present in severe respiratory distress with inadequate oxygenation or ventilation need the immediate establishment of an airway. Because they may have lesions that make intubation difficult or impossible, it is necessary to have available experienced personnel, including an anesthesiologist and otolaryngologist. Fiberopticassisted intubation may be necessary and also may be helpful in establishing the etiology of stridor.

In patients who appear stable, a brief history may help in differentiating the causes of stridor. Gradual onset of symptoms over weeks or months, especially if accompanied by constitutional symptoms, would suggest neoplasm. Stridor that occurs in hours or days, especially if the patient is febrile, is suspicious for an infectious etiology, such as epiglottis croup or abscess. A history of previous intubation is quite important because subglottic stenosis may not appear for months after a traumatic or prolonged intubation. Close questioning regarding episodes of choking or coughing while eating may raise the possibility of aspiration. Foreign body in either the airway or esophagus may cause stridor, especially in younger patients. Pressure exerted from an esophageal foreign body may partially obstruct the airway (20).

Physical examination of a patient with stridor typically begins with the examiner's unaided ear. Loud, noisy breathing is heard. The patient's respiratory rate, depth of respiration, use of accessory muscles of respiration, level of alertness, and evidence of cyanosis should be observed. Inability to handle oral secretions should be noted because it may suggest peritonsillar abscess, retropharyngeal hematoma or abscess, epiglottis, or foreign body.

Palpation of the airway should be performed to assess for crepitation, suggesting subcutaneous emphysema. A displaced trachea or firm mass could indicate tumor or goiter. Lymphadenopathy could suggest neoplasm. Auscultation of the entire airway may help localize the anatomical location of the lesion; so one should listen especially carefully over the larynx, extrathoracic trachea, and central chest.

Radiological studies of the chest, as discussed earlier in this chapter, should be obtained to evaluate stridor in stable patients. In addition, anterior-posterior and lateral radiographs of the neck should be obtained. If more detailed imaging of the airway is needed, CT scans should be obtained. Spirometry with flow-volume loops, as discussed in evaluation of tracheobronchial obstruction, may be an important aid in evaluation of stridor.

Therapy

Stridor secondary to infectious etiologies requires treatment with appropriate antimicrobial therapy. Hemophilus influenza is the most common bacterial cause of epiglottitis, although its incidence has been declining steadily. Respiratory syncytial virus infection may cause airway edema resulting in stridor. This infection is typically seen in children, although the virus has been recovered in immunocompromised adults. Treatment with the antiviral drug ribavirin may be considered in the acutely ill patient. Anaerobes, streptococcal species, and a wide assortment of less common agents may cause abscess formation, leading to airway obstruction. While waiting for the culture results, it is appropriate to treat the patient with broad-spectrum antibiotics.

Several therapies are available to stabilize the stridorous patient who is clinically decompensating. Heliox, a mixture of helium and oxygen, has been useful in improving oxygenation, ventilation, and decreasing work of breathing in patients with stridor from a wide variety of causes (21,22,23 and 24). These causes included postextubation edema, extrinsic compression from tumor, and status asthmaticus. Because heliox has a lower density than ambient nitrogen-oxygen gas mixture, there is decreased airway turbulence and airway resistance. The typical heliox mixture varies from helium 60%-oxygen 40% to maximal concentration helium 80%-oxygen 20%. It can be delivered via a tightfitting face mask, and relief of respiratory distress is often immediate. Treatment with high-dose intravenous (i.v.) corticosteroids should be started using methyl prednisolone 1 mg/kg every 6–8 hours. Racemic epinephrine 2.25%, 0.5 ml in 2.5 ml saline delivered via hand-held nebulizer as often as hourly, but usually every 3–4 hours, may be used especially for postextubation stridor (25).

Noninvasive mask ventilation with continuous positive airway pressure or bilevel positive airway pressure may decrease the work of breathing and overcome large airway obstruction, although currently no studies have evaluated the efficacy of this therapy. Close coordination with a respiratory therapist is needed if this therapy is initiated. Either a tight-fitting mask over the nose or nasal pillars applied to the nares may be used. Positive pressure of 5 cm H_2O is started and titrated up to a maximum of 20 cm H_2O. Most patients are unable to tolerate higher pressures. If needed, supplemental oxygen and humidification can be “bled” into the positive pressure system. Finally, endotracheal intubation or tracheostomy should be considered in appropriate clinical situations for patients severely affected.

BRONCHOSPASM

Bronchospasm is the state of abnormal narrowing of the airways and is usually episodic. Airflow is obstructed and becomes turbulent, resulting in severe dyspnea. Patients complain of dyspnea, chest tightness, or pressure, although occasionally cough is the only symptom. Exacerbation of symptoms frequently occurs in the early hours of the morning, when bronchial tone is normally increased. Wheezing is heard on auscultation of the chest, occasionally needing to be provoked by forced expiration or deep breathing. Expiration time is usually prolonged. Patients may use accessory muscles of respiration and pursed lip breathing.

Bronchospasm is the end result of airway narrowing, which is believed to be a consequence of a state of hyperresponsiveness of the airways to a wide variety of stimuli (26). More recently, airway inflammation has been considered of prime importance in the development of airway hyperactivity. The airway epithelium is thickened and friable, and microscopically there is infiltration with inflammatory cells, especially eosinophils and mast cells. Mucous glands are hyperplastic, and goblet cells are more numerous compared with normal persons (27). Bronchial lavage fluid of the lung reveals high concentrations of cytokines, prostaglandins, histamine, triptase, and immunoglobulin E (26). In severely affected persons, the airways may be plugged with excessive inflammatory secretions and desquamated epithelium (28). Airway muscle is both hyperplastic and hypertrophied, but it has been found to contract normally when stimulated (29). Smooth-muscle mass is increased, probably in response to growth factors, such as histamine, or as a result from increased work (30,31).

Evaluation

The differential diagnosis for bronchospasm includes asthma, COPD, upper/large airway obstruction (see the section Tracheobronchial Obstruction) congestive heart failure, bronchiolitis (infectious or inflammatory, medication induced), lymphangitic tumor spread, or rarely, pulmonary embolism. Multiple etiologies for bronchospasm are common in an individual patient. The extent of evaluation depends on the complexity of an individual patient's medical condition. In a patient with a significant smoking history, chronic sputum production, and diffuse bronchospasm on examination, it is likely that an exacerbation of COPD explains the clinical situation. Obviously, in a patient who has a similar history but is immunocompromised, the diagnostic possibilities must be widened.

Chest radiographs should be obtained in patients presenting with bronchospasm. Bronchial wall thickening, flattened diaphragm, and increased retrosternal air space are consistent with hyperexpansion and air trapping and would support the diagnosis of asthma or COPD. In addition, the chest radiograph may reveal complications of obstructive lung disease, such as pneumonia, pneumothorax, or atelectasis.

A chest radiograph with no change from the patient's baseline film or with atelectasis or small pleural effusion should alert the clinician to possible pulmonary embolism, and a ventilation/perfusion scan ( ) should be obtained to access for pulmonary embolism. The scan needs to be compared with the chest radiograph for accurate interpretation. A completely normal perfusion scan effectively excludes pulmonary embolism. Segmental perfusion defects in areas of normal ventilation define a high probability scan, which indicates an 85–90% probability of pulmonary embolism, which must be interpreted with care, as one of the few causes of false-positive scans is bronchospasm. Helical CT scanning of the chest may be more cost effective and more accurate than scanning in identifying clinically significant pulmonary emboli (32). Again, if the clinical situation warrants further evaluation, noninvasive testing to detect lower extremity deep venous thrombosis or pulmonary angiography may need to be pursued.

Spirometry not only confirms airway obstruction but can suggest its anatomical location (upper versus intrathoracic) and quantify the extent of airway obstruction. In addition, it also may be helpful in monitoring treatment response. Forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV_1) are reduced in an obstructive lung defect with the reduction in FEV_1 greater than that of FVC. In airway obstruction, the ratio of FEV_1 to FVC will be less than 70%. The severity of the obstructive defect is graded by the patient's percentage of predicted FEV_1 (70% or greater, mild; between 60–70%, moderate; between 50–60%, moderately severe;

between 35–50%, severe; and less than 34%, very severe) (33).

The contour of the expiratory portion of a flow-volume loop shows concavity, which worsens with the extent of the obstructive lung defect. Patients with chronic obstructive lung disease have fixed airway obstruction but can have some degree of variability in FVC and FEV_1 during exacerbations. On the other hand, most patients with asthma should have normal or near normal spirometry between episodes of illness. Spirometry often is obtained before or after use of inhaled bronchodilators. Patients who have at least a 15% improvement in FVC or FEV_1 and 200 ml absolute increase in FVC or FEV_1 are considered to have a significant immediate response. This group is considered to benefit most from inhaled bronchodilators and corticosteroids, although many studies have reported conflicting results regarding this issue (34). Patients who do not improve immediately after inhaled bronchodilators may have spirometric or clinical improvement with regular use; therefore, these medications should not be withheld.

Therapy

The goals of therapy in bronchospasm are to dilate the distal airways and reduce inflammation, hence relieving airway obstruction. There are many pharmacological agents available to treat bronchospasm (Table 27-3). The severity of the patient's symptoms guides which of these medications are used and in what order. Beta adrenergic agonists continue to be important pharmacological agents to relieve bronchospasm. They can be administered in many forms: inhaled through metered-dose inhalers, inhaled through hand-held nebulizers, taken orally, or injected subcutaneously or intravenously. Over the past decade, there has been a strong movement against using oral beta agonists as their efficacy is similar to the inhaled forms but they have a higher incidence of side effects. Subcutaneous forms are used sparingly for emergency treatments. Intravenous administration of isoproterenol is no longer recommended (35).

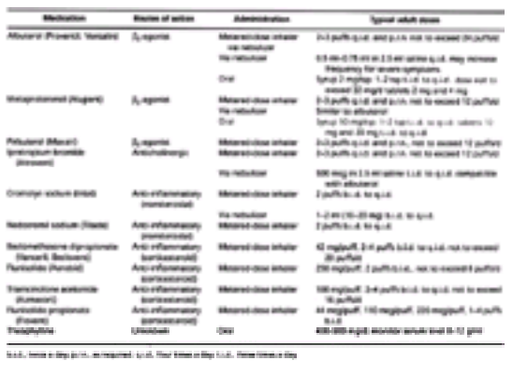

TABLE 27-3. MEDICATIONS COMMONLY USED TO TREAT BRONCHOSPASM

Beta adrenergic agents promote airway smooth-muscle relaxation by a mechanism that is not completely understood. In addition, they increase mucociliary clearance and increase the secretion of electrolytes by the airways. Side effects include tremor, tachycardia, palpitations, hypokalemia, and hyperglycemia. Usually these side effects are most pronounced when the medications are first initiated and lessen over time. Sustained-release, oral, beta-adrenergic agonists have a useful role in patients with significant nocturnal symptoms. Patients with mild bronchospasm may be started on beta-adrenergic agonists alone to control symptoms. For patients with more severe presentations, other therapies are needed. The recent trend has been to have patients use these medications on an as-needed basis for mild symptom control. Recent studies have found equal efficacy between metered-dose inhalers and nebulized beta adrenergic agents if proper technique is used and the dose is increased to five or six inhalations. Some patients benefit by using a spacer device to improve delivery with metereddose inhalers. The total dose of beta-adrenergic agonist should be 24 or fewer inhalations in a 24-hour period to prevent tachyphylaxis. Patients who do not find relief with use of beta-adrenergic agonists or who must increase their usual dose should be evaluated for additional therapies. The recent spate of literature on the safety of beta-adrenergic agonists found that mortality increased when patients were undertreated for asthma (36,37,38 and 39).

Anticholinergic agents act by decreasing parasympathetic bronchoconstriction of the airways. They are most useful in COPD, in which parasympathetic activity is believed to be greater than normal. Ipratropium bromide is the only anticholinergic agent available for inhalational use in the United States. Because of recent reports suggesting ipratropium bromide may be more effective than betaadrenergic agonists in promoting bronchodilation in patients with COPD, some authors believe it should be the first agent used in maintenance therapy in COPD (40,41 and 42). Corticosteroids are widely used in the treatment of bronchospasm. Patients with mild to moderate symptoms may benefit from inhaled corticosteroids. They are especially attractive because they act locally, with minimal absorption and limited toxicity. However, reports of hypothalamic-pituitary-adrenal axis suppression and cataract formation were recently reported with the use of high dose inhaled corticosteroids (43). In addition, patients should be cautioned that these medications must be used regularly and may take weeks for therapeutic effect. Therefore, corticosteroids should not be used as monotherapy for acutely symptomatic patients. Inhaled corticosteroids also may allow patients on systemic corticosteroid therapy to have their doses reduced or discontinued altogether. Patients with more serious symptoms or those in respiratory distress require systemic corticosteroids. These medications may take up to 12 hours to have clinical effects. Prednisone, 0.5–1.0 mg/kg per 24 hours, may be used for 1–2 weeks and then gradually tapered. Seriously ill patients should receive methyl prednisolone, 1–2 mg/kg every 6–8 hours i.v., until improvement is noted. At that time, the i.v. dose may be tapered over several days and the patient switched to oral corticosteroids. Peak flow meters along with physical examination and arterial blood gases help determine a patient's response to therapy.

Besides corticosteroids, cromolyn sulfate and nedocromil sodium are other antiinflammatory agents. Their exact mode of action is unclear, but likely they act as mast cell stabilizers. These medications are particularly useful in children for symptoms related to exercise or cold air and for patients with a strong allergic component to their bronchospasm. Cromolyn sulfate is available as a metered-dose inhaler, two puffs four times a day, or inhalational solution, 1–2 cc four times a day via nebulizer. Nedocromil sodium is used two puffs four times daily via metered-dose inhaler. Again, patients must be educated to use these medications regularly because its maximal effects are not noted for 4–6 weeks.

Theophylline, once a mainstay of therapy, has lost its place as a first-line therapy in the treatment of bronchospasm because of excessive toxicity and potential for serious drug interactions. It is still used in patients with COPD in an effort to augment respiratory muscle function and for its weak bronchodilator effects. In addition, it is used in corticosteroid-dependent asthmatics in hopes of decreasing their daily steroid dose (44). Typically, patients are started on long-acting preparations at a dose of 400–900 mg/day to achieve serum levels of 8–12 µ/ml. The dose must be individualized depending on concurrent medications, smoking history, and medical history, such as congestive heart failure, as all of these change drug clearance. Critically ill patients in respiratory failure secondary to bronchospasm who do not respond to maximal therapy, including intubation and mechanical ventilation, should be considered for bronchial muscle relaxation with inhalational anesthetics.

COUGH

Etiology

Cough is a protective, complex reflex that helps clear the airways of foreign material or excessive secretions. It is a common problem that translates into 30 million physician visits per year and millions of dollars spent on over-the-counter medications (45).

The cough reflex is complicated and not fully understood. Suffice it to say that cough results from stimulation of cough receptors, which may be found in the larynx, respiratory epithelium, tympanic membranes, esophagus, pericardium, and sinus mucosa. Afferent impulses travel via the vagus, trigeminal, glossopharyngeal, and phrenic nerves to cough centers in the medulla. Efferent impulses travel via the vagus, phrenic, and spinal nerves to the glottis and respiratory muscles, which produce the high-velocity flow of air that defines a cough (46,47).

Evaluation

Cough is a common complaint in patients with advanced cancer. In the cancer patient, cough may be secondary to endobronchial tumor, pericardial disease, vocal cord paralysis, or aspiration. Cough also may be due to complications of treatment, such as radiation pneumonitis or chemotherapyinduced interstitial disease (48). In addition, patients with underlying cancer may have all the same causes of cough found in the general population. The most common etiologies of chronic cough include postnasal drip syndrome, asthma, and gastroesophageal reflux (49,50).

A detailed history and physical examination are most helpful in determining the cause of chronic cough (47). Chest radiographs should be obtained early in the evaluation of cough (51). In patients who chronically produce sputum or in whom there is a suspicion of interstitial lung disease, a high-resolution chest CT scan may be helpful. Of patients with interstitial lung disease, 10–15% have a normal chest radiograph. Computed tomography scan is very helpful in the evaluation of

bronchiectasis.

Sinus imaging, including radiographs and CT scanning, are needed to evaluate for chronic sinus disease. Some authors recommend a trial of antihistamine-decongestants before pursuing sinus radiographical studies (45). Spirometry, before and after inhaled bronchodilators and methacholine challenge, help to evaluate for asthma or chronic obstructive lung disease. Evaluation for gastroesophageal reflux disease can be undertaken with barium esophagography or 24-hour esophageal pH monitoring. Finally, if no cause has been found for chronic cough, bronchoscopy should be considered to evaluate for occult foreign body aspiration or small endobronchial lesions, such as carcinoid tumors or bronchogenic cancer, although studies have found this to be of low yield (49).

Therapy

Treatment of cough is most successful if it is tailored to a specific etiology. Postnasal drip syndrome may be well controlled with the use of antihistamine-decongestant therapy. Asthma therapy was discussed earlier in this chapter (see section on Therapy under Stridor) Gastroesophageal reflux disease is treated with H_2 receptor blockers or proton pump inhibitors along with lifestyle changes. In patients for whom no cause is found for their cough or it is due to airway involvement with tumor, empiric medical therapy is reasonable. Some patients obtain relief with the use of b_2-adrenergic agonists such as Albuterol, two or three inhalations every 4–6 hours or 0.5 ml Albuterol solution in 2 ml saline via nebulizer every 4–6 hours.

For generations, opiates have been used and are variably effective antitussives (46,52). There is no evidence of superior antitussive effect with one preparation over another. Codeine, 15–30 mg every 4–6 hours, is a reasonable starting dose, with titration upward to control symptoms if the side effects are tolerable. Nonnarcotic cough preparations, such as guaifenesin and dextromethorphan, may be tried, although they have been only weakly effective. Two recent articles review the many conflicting studies evaluating overthe-counter and prescription cough medications (52,53).

Inhaled lidocaine is used to suppress cough during bronchoscopy. Animal studies and a few human studies suggest that lidocaine has an antitussive effect when inhaled via nebulizer, probably acting on afferent C-fibers in the larynx and trachea. The dose is empiric; a starting dose is 5 ml of 2% lidocaine solution every 4 hours via hand-held nebulizer (46,48). Patients should be cautioned regarding anesthesia of the oropharynx and larynx, which puts them at risk for buccal injury or aspiration. The dose may be increased if needed, but there are no studies giving explicit guidelines for this therapy. Generally, during bronchoscopy, doses higher than 300 mg of lidocaine (15 ml of 2% solution) are avoided to decrease the risk of seizures, as there is significant systemic airway absorption of lidocaine.

In patients who have underlying chronic bronchitis, a trial of inhaled ipratropium bromide, two puffs four times a day, may diminish the cough (54). Finally, some patients respond to corticosteroids. Some of these patients have underlying asthma, whereas others may have other reasons for airway inflammation, such as chronic bronchitis, bronchiectasis, or radiation pneumonitis. Inhaled steroids such as flunisolide two puffs twice daily and triamcinolone two to four puffs four times a day may be tried as initial therapy or maintenance therapy after oral agents. Patients not responding to inhaled therapy should be tried on prednisone, 0.5–1.0 mg/kg per day for 2–4 weeks. If the cough subsides, the prednisone should be tapered to the lowest dose to control symptoms, or patients should be switched to inhaled steroids.

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28

MANAGEMENT OF PLEURAL AND PERICARDIAL EFFUSIONS

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One of the most common and troubling problems for the cancer patient is the development of a malignant effusion of any body cavity. When it occurs in the pleural cavity or the pericardium, this abnormal accumulation of fluid may cause severe symptoms or may even be life threatening. Any type of cancer can metastasize to these serous cavities, and this problem is most common in disseminated malignancies. Although the development of a malignant pleural or pericardial effusion almost always indicates that the patient has an incurable cancer, prompt recognition and diagnosis followed by appropriate treatment can result in excellent palliation and a marked improvement in the patient's quality of life. In addition, it is critical that an accurate diagnosis is made to establish the malignant cause of the effusion, because cancer patients can often develop an effusion from a benign cause such as radiation therapy, infection, chemotherapy, or heart failure. All cancer patients with pleural or pericardial effusions, especially when associated with symptoms, deserve a thorough evaluation and an opportunity for prompt therapy.

PLEURAL EFFUSIONS

Incidence

In a general hospital patient population, 28–61% of all pleural effusions are malignant; the highest incidence is in the over-50 age group (1,2,3 and 4). A malignant pleural effusion is the initial manifestation of cancer in 10–50% of patients (4,5). In patients with known breast cancer, almost half will develop a malignant effusion during the course of their illness (3), although this figure may be somewhat lower now with more recent treatment regimens. For lung cancer, 7–15% of all patients develop this complication (5). Eventually, about half of all disseminated cancer patients develop a malignant pleural effusion (4). Overall, this is a highly significant clinical problem, because approximately 100,000 malignant pleural effusions occur annually in the United States (6). Table 28-1 lists the frequency of the various tumor types that are associated with malignant pleural effusions. The tumor origin is not found in 15% of effusions. In such cases the cell type is usually metastatic adenocarcinoma with the primary site unknown.

Tumor type	Incidence (%)
Lung	35
Breast	23
Lymphoma/leukemia	10
Adenocarcinoma, unknown primary	12
Reproductive tract	6
Gastrointestinal tract	5
Genitourinary tract	3
Primary unknown	3
Other cancers	5

From Hausheer FH, Yarbro JW. Diagnosis and treatment of malignant pleural effusion. *Semin Oncol* 1985;12:54–75, with permission.

TABLE 28-1. TUMOR CAUSES OF MALIGNANT PLEURAL EFFUSIONS FROM COLLECTED SERIES

The appearance of a symptomatic, malignant, pleural effusion in a patient with known cancer significantly alters his or her quality of life. Although it is reported that up to 25% of patients with an effusion are asymptomatic, this may prove to be an overestimate if a careful history is elicited (7). In general, a prompt diagnosis accompanied by timely treatment of the effusion can markedly enhance the patient's functional status and should be considered early after the development of this common complication of advanced cancer.

Etiology and Pathophysiology

The pleura is a serous membrane that invests each lung to form a closed sac called the *pleural cavity*. There is a continuous passage of an almost protein-free fluid (protein content, 1.5 g/dl) through the pleural membrane thought to be based primarily on hydrostatic and colloid osmotic pressures. The net pressure in the parietal pleura is 9 cm H_2O, favoring movement of fluid into the pleural cavity, which is balanced with a net 10 cm H_2O pressure in the visceral pleura, favoring absorption of pleural fluid by the visceral capillaries. Therefore, the overall direction of movement of fluid is from the systemic circulation in the parietal pleura across the pleural cavity back into the pulmonary circulation in the visceral pleura. At any one time, either pleural cavity has only 2–5 ml of fluid present, although as much as 5–10 liters flow through this space in any 24-hour period (8,9). Any imbalance in these pressures that disturbs the normal equilibrium may lead to a net accumulation of fluid in the pleural cavity.

Traditionally it has been held that the normal equilibrium may be interrupted, leading to the accumulation of an effusion. Some of these changes that may occur include the following:

- Increased capillary permeability due to inflammation from infection or tumor cell implantation
- Increased oncotic pressure of fluid in the pleural space from the inflammatory reaction from tumor cells or infection
- Decreased systemic oncotic pressure due to hypoalbuminemia from malnutrition
- Increased negative intrapleural pressure due to atelectasis, possibly from tumor obstructing a bronchus
- Increased hydrostatic pressure in the pulmonary circulation, as in congestive heart failure from cardiac or pericardial metastases

In addition, a malignant effusion may result from obstruction of the visceral or parietal lymphatic channels by tumor, resulting in impaired absorption. Most malignant effusions are probably the result of a combination of the factors, with an overall increase in fluid production and a decrease in absorption (3,10,11).

More recently, the role of vascular hyperpermeability as mediated by vascular endothelial growth factor (VEGF) has received increasing attention. Fidler's group at M. D. Anderson has demonstrated that pleural invasion by malignant cells expressing VEGF mRNA is required for production of malignant effusions and that the effusions (but not tumor growth) could be abrogated by transfection of the cells with an antisense VEGF (12). PTK 787, a compound that blocks VEGF receptor tyrosine kinase phosphorylation (among other receptor tyrosine kinases) leads to reduced pleural fluid formation but not to reduced proliferation of the tumor cells (13). Several investigators have described increased levels of VEGF in the fluid of patients with malignant effusions (14,15,16,17,18 and 19) and the presence of increased FLT-1 VEGF receptors (fms-like tyrosine kinase receptor of VEGF) on mesothelial cells (15). A Dutch group has demonstrated that antibodies against VEGF or SU5416, a small molecule tyrosine kinase inhibitor, can also block production of both pleural and peritoneal fluid accumulation *in vitro* (20). Although still in an early phase of understanding, the role of vascular hyperpermeability may explain why some agents that do not induce brisk fibrosis in the pleural space may still be useful in the treatment of malignant effusions (21).

Pleural effusions caused by a malignancy usually result in an exudate with a high protein content, although rare exceptions have been reported (1,5). However, transudative effusions (low protein) may occur as the indirect result of an advanced cancer, as in the patient with malnutrition and hypoalbuminemia, congestive heart failure due to cardiac failure, or liver disease secondary to metastases (3).

Clinical Presentation

The most critical initial step in evaluating the patient with a suspected malignant pleural effusion is to take a complete history and perform a careful physical examination. This simple step will usually exclude other causes of an effusion, such as heart failure or infection.

The clinical presentation of a malignant pleural effusion is almost always related to collapse of lung from the increased pleural fluid and the resulting initial symptom of exertional dyspnea. Later, resting dyspnea and orthopnea develop as the effusion increases in volume. A dry, nonproductive cough, a sense of heaviness in the chest, and occasionally pleuritic chest pain are also experienced. Nevertheless, an occasional patient (<25%) will appear completely asymptomatic in the face of a large effusion (11).

The physical findings of a malignant pleural effusion often include dullness to percussion of the affected hemithorax, decreased vocal fremitus, decreased breath sounds, egophony, and no demonstrable diaphragmatic excursion. Rarely, a very large effusion will result in a mediastinal shift with contralateral tracheal deviation and possibly even plethora or cyanosis from partial caval obstruction (3,7). Other signs and symptoms may be present initially but are usually related to the underlying primary tumor and not the effusion.

Diagnosis

The approach to the diagnosis and subsequent treatment of a patient with a suspected malignant pleural effusion is shown in Figure 28-1.

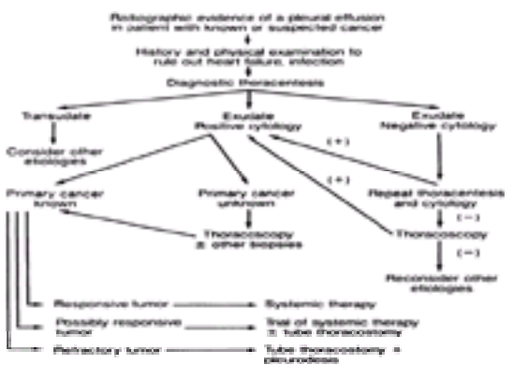

FIGURE 28-1. Approach to the diagnosis and treatment of malignant pleural effusions. +, study result is positive; –, study result is negative. (From Ruckdeschel JC. Management of malignant pleural effusion: an overview. *Semin Oncol* 1988;15:24–28, with permission.).

The initial screening examination is the posterior-anterior chest radiograph, including decubitus views, which will confirm the presence of free pleural fluid and will also suggest the presence of any loculated fluid. An upright posterioranterior chest radiograph that demonstrates blunting of the costophrenic angle will detect 175–500 ml of fluid, while a decubitus view will show as little as 100 ml (22).

Computed tomography (CT) may play a role in the evaluation of malignant pleural effusion patients. This is especially necessary if the hemithorax is opaque on chest radiograph, when a mesothelioma is suspected, or when the underlying primary tumor is unknown. However, a large effusion often obscures an underlying tumor in the lung, and CT may prove more useful after drainage of the effusion and lung reexpansion. Occasionally, chest ultrasonography may prove useful in differentiating between pleural fluid and pleural thickening (23), but its more common application is to localize small effusions as a guide in thoracentesis (24).

After confirmation of a pleural effusion radiographically and after exclusion of any obviously nonmalignant causes, the next step is a diagnostic thoracentesis. In general, when a malignant effusion is suspected, only a small amount of fluid is withdrawn for diagnosis (at least 250ml is needed for cytology). This leaves a moderate amount behind so that insertion of a chest drainage tube later is easier.

The use of a disposable thoracentesis kit with a specially designed multihole catheter is preferred, because it tends to lessen the chance of complications such as a pneumothorax. Rapid removal of a large amount of fluid, especially over 1,500 ml, is not advised, because this may result in life-threatening reexpansion pulmonary edema, a real and not infrequent complication of large-volume thoracenteses (25).

The fluid removed should be heparinized and sent to the lab for protein and lactic acid dehydrogenase (LDH) determinations and cytology. Other tests, including pH determination (for which the fluid must be collected in an anaerobic container), glucose level, cell count, and cultures with smears, are often obtained, although they are not necessary. With a malignant pleural effusion, the pH and glucose level are often low, but these are nonspecific findings (3). A malignant effusion is frequently hemorrhagic (erythrocyte count >100,000/mm^3), but this is also nonspecific and occurs in only one third of cases (5). The Health and Public Policy Committee of the American College of Physicians has demonstrated that elevated levels of LDH or protein in the fluid, and ratios of fluid to concurrent serum levels of LDH and protein, are all that are required for the distinction of a transudate from an exudate (Table 28-2) (26). If the fluid is found to be a transudate, then a malignancy is essentially excluded. An exudate with a negative cytology result demands a second diagnostic thoracentesis with cytology, which will add approximately 6–11% more malignant diagnoses (3).

Test	Positive predictive value (%)
(1) Fluid LDH >200 international units	100
(2) Fluid/blood LDH ratio >0.6	99
(3) Fluid protein >3 g/dl	95
(4) Fluid/blood protein ratio >0.5	99
(1), (2), or (4) above	99

LDH, lactic acid dehydrogenase.
Reprinted from Matsuyama W, Hashiguchi T, Mizoguchi A, et al. Serum levels of vascular endothelial growth factor dependent on the stage progression of lung cancer. Chest 2000;118(4):948–951, with permission.

TABLE 28-2. DIAGNOSTIC TESTS CONFIRMING THE PRESENCE OF AN EXUDATE

Cytology is the best method of diagnosing a malignant pleural effusion, although it is somewhat dependent upon tumor type, the experience of the cytopathologist, and the amount of fluid that is sent for cytologic analysis; at least 250 ml is preferred for the best yield (27). In patients with an effusion eventually proved to be malignant, the first cytology result will be positive in 53–59% of cases, rising to 65% when a second thoracentesis is performed (3). In some tumors, such as Hodgkin's disease, the rate of positive cytology results is relatively low at 23%, while with others, such as breast or lung cancer, the diagnosis rate is as high as 73% (3). A variety of immunocytochemical staining techniques and, recently, cytogenetic markers have been added to complement the standard cytologic techniques. These methods have resulted in some increased diagnostic yield, although they often lack sensitivity and specificity, and also the laboratory expense is increased (3,10). We do not recommend using these tests outside of a clinical trial.

If the result of cytologic examination is negative, traditionally a blind pleural biopsy has been attempted, with some expectation of increased diagnostic yield. Although a blind biopsy may be a sensitive test in pleural tuberculosis because of its diffuse involvement, malignancies involving the pleura are commonly patchy in distribution, and a blind pleural biopsy usually adds little to the diagnosis. Although earlier series suggest that the pleural biopsy may be valuable in diagnosing malignancy in a patient with negative cytology results (3), a more recent direct comparison of pleural fluid cytology versus blind pleural biopsy casts doubt on its benefit. In this important series (28), cytology results were diagnostic of cancer in 71% of cases and suggestive in another 8%. Blind biopsy of the pleura gave positive results for malignancy in 45% of cases but provided a diagnosis in only 3% of cases where the cytology result was nondiagnostic.

Therefore, if two exudative pleural fluid cytology results are negative for malignancy, most clinicians now bypass the blind pleural biopsy and move promptly to video-assisted thoracoscopy (VATS), wherein visually directed pleural biopsies are readily obtained and the diagnostic yield is quite high. In large series, the diagnostic sensitivity of VATS with malignant pleural effusion is 97% (29). Although VATS is a surgical procedure usually requiring general anesthesia, the mortality and morbidity is quite low at 0.5% and 4.7%, respectively (30).

In addition to providing a high diagnostic yield of malignancy by directed biopsies during VATS, this procedure, when the ipsilateral lung is collapsed and the patient is under general anesthesia, permits direct definitive therapeutic intervention with lysis of adhesions, mechanical pleurodesis, pleurectomy, or talc poudrage, with a very low recurrence rate (31). Finally, when the fluid cytology result is positive but the primary site is unknown, VATS may be employed occasionally to obtain a larger amount of tissue for more definitive studies or to rule out the presence of a mesothelioma, especially when “adenocarcinoma, unknown primary” is the working diagnosis according to cytology. The advent of VATS has virtually eliminated the need for diagnostic open thoracotomy when a malignant effusion is suspected.

Prognosis

Once the diagnosis of a malignant pleural effusion has been made, the choice of therapy must be put in perspective with the extent of the tumor, the condition of the host, and the prognosis. Virtually all of these patients have an incurable disease, so the treatment must be aimed at the most effective palliation for maximal, comfortable time outside of the hospital. For all patients, the overall mean survival time is 3–6 months. The mortality is as high as 54% at 1 month and rises to 84% at 6 months (11,33). Some malignant effusion patients with responsive tumors, such as breast cancer, may have a longer survival averaging 7–15 months (11); 20% have a 3-year survival (32). Ovarian cancer patients with a malignant effusion also have a longer expected mean survival of 9 months (23). Conversely, lung cancer patients have a worse prognosis, with a mean survival of 2 months, and 66% will die by 3 months (11).

Treatment

Systemic Therapy

When the effusion is small and asymptomatic and the tumor is likely to be sensitive to systemic therapy, as with lymphoma, leukemia, breast cancer, ovarian cancer, small cell lung cancer, or germ cell tumors, the first line of therapy should be systemic chemotherapy or hormonal therapy, preceded by thoracentesis if the patient is symptomatic (7,10). When the tumor is relatively chemoresistant or has been shown to be so in the past, as with non-small cell lung cancer or pancreatic cancer, the choice then is for prompt tube thoracostomy followed by intrapleural therapy. Table 28-3 lists methods of controlling malignant pleural effusions.

Systemic chemotherapy
Repeated thoracentesis
External radiotherapy
Tube thoracostomy alone
Tube thoracostomy with drug instillation
Pleurectomy
Pleuroperitoneal shunt
Videothoracoscopy with pleurodesis

TABLE 28-3. METHODS OF CONTROLLING MALIGNANT PLEURAL EFFUSIONS

Thoracentesis

Thoracentesis alone may relieve symptoms briefly, but the fluid usually reaccumulates rapidly. In a study of 94 patients, the mean time to reaccumulation of the pleural effusion after thoracentesis was 4.2 days, and 97% had a recurrence of the fluid by 1 month (34). In addition, repeated thoracenteses carry the risk of empyema, pneumothorax, a trapped lung from inadequate drainage and loculation of fluid, and the real possibility of progressive malnutrition from repeated removal of a large amount of the high-protein effusion fluid.

Radiation Therapy

Radiation therapy may occasionally be useful as primary therapy, but only when directed at paramalignant effusions caused by mediastinal lymphadenopathy and lymphatic obstruction (35). Improvement is rarely seen before 3 weeks, and therefore radiation has little application in the more acutely symptomatic effusion.

Tube Thoracostomy

Tube thoracostomy alone has been proposed as effective therapy for malignant effusions (3). But careful review of the results demonstrate that none of these older studies reliably supports the conclusion that chest tube drainage alone is efficacious in long-term control (3). However, tube thoracostomy appears quite useful in draining the pleural cavity and maintaining opposition of the pleural surfaces when a therapeutic agent is subsequently instilled into the chest for sclerotherapy. Anderson and associates found that chest tube drainage greatly improved the response to intrapleural nitrogen mustard, compared with instillation of the agent after thoracentesis alone (34). The relative direct antitumor effect of any of the sclerosing agents is probably little, or at best some agents are cytostatic (36) and their primary action is mostly local inflammation.

Recently, some enthusiasm has been voiced for the use of small-bore (8 French or 12 French) catheters for gravity drainage or even suction drainage of the pleural cavity followed by intracavitary sclerotherapy. The long-term results of this technique are still undetermined (37), although the selection of patients with free-flowing effusions can enhance the outcome significantly (38). These small-bore catheters rapidly become occluded from debris and fibrin clots, and generally effective suction can be maintained in the pleural cavity for only a few hours. If, as it is thought, the visceral and parietal pleurae should be kept in direct opposition for a day or two after instillation of the sclerosing agent to obtain a pleurodesis, then it is unlikely that these small catheters will be as successful as larger chest tubes.

To achieve the best palliation, the pleural cavity should be drained completely and the lung fully expanded. This is best accomplished by closed tube thoracostomy. A no. 24 French or 28 French chest tube is usually inserted in the sixth or seventh interspace in the midaxillary line with the tube directed posterior to the lung to maximize drainage. Generally the patient is given 3–6 mg morphine sulfate intravenously just before the procedure for sedation and to allay anxiety. The patient is positioned supine but turned up with the appropriate side of the chest elevated at 45–60 degrees and with the physician standing behind the patient. After sterile prepping and draping of the skin, 20–40 ml 1% lidocaine is infiltrated into the skin, the subcutaneous tissue, and most important into the intercostal musculature and pleura of the interspace where the tube will enter. A brief thoracentesis is always performed first at the planned pleural entrance interspace to make sure that there is

free aspiration of fluid. If no fluid is obtained, the chest tube entrance site must be altered to a place where fluid is readily obtained by thoracentesis. A small 2- to 3-cm skin incision is made 1.0–1.5 interspaces below the target interspace, and a subcutaneous tunnel is created bluntly with a clamp. Likewise, the pleural cavity is initially entered with a blunt clamp, which is spread wide to create a generous opening for the chest tube. A clamp is placed on the introductory end of the chest tube to pass the tube through the subcutaneous tunnel into the pleural space and to direct the tube posterior and cephalad. The opposite end of the tube is also clamped off during the insertion to avoid an open pneumothorax and a gush of fluid from the chest. The physician should slowly twirl the tube as he passes it into the chest so he can avoid kinking the tube, because the tube will not twirl easily if it bends over inside the chest cavity. As long as the tube remains straight, it will twirl easily. Once the tube is inserted to a predetermined depth based on numerical markings on the tube itself, it is firmly sutured into place to the skin with heavy silk suture (0-silk or larger). The tube is then attached to an underwater seal drainage device at approximately 20 cm H_2O suction. If there is a very large effusion, it should not be all drained immediately. Instead, 1,000–1,500 ml should be drained initially, and then the tube should be clamped for 30–60 minutes, draining approximately 1,000 ml every 60 minutes until the chest is completely empty. More rapid drainage of a large pleural effusion encourages the development of the life-threatening problem of reexpansion pulmonary edema, a real and preventable phenomenon (25). Although some physicians use a trocar chest tube, the risks of laceration of the lung or even the heart or diaphragm are significant.

Chest radiographs are obtained initially and then daily as long as the tube is in place. The chest tube is left on suction for total drainage of the effusion and to encourage reexpansion of all possible lung. When a properly positioned chest tube is completely open and is on suction, essentially all of the fluid that is drainable will have drained within a few hours of insertion and certainly after overnight drainage. Likewise, all lung that is expandable and is not trapped will have expanded after overnight suction. Although some authors suggest waiting an indefinite period of time until the chest tube drainage has decreased to an arbitrary 100 ml per 24 hours (10), waiting this extra time is probably not necessary and may even lessen the chance of success. The prolonged presence of the tube irritating the pleural cavity may encourage loculations and lessen the eventual distribution and effectiveness of the sclerosing agent. Therefore, the decision when to instill the intracavitary agent should rest on the appearance of the chest radiograph and not the daily drainage. Usually, the best time to instill the sclerosing agent is the day after chest tube insertion.

Fibrinolytic Agents

If the chest radiograph the day after chest tube insertion shows apparent residual fluid, and especially if the fluid is thick or gelatinous, it may be worthwhile to try intrapleural instillation of urokinase 100,000 units in 100 ml 0.9% saline, clamping of the tube for 6 hours, and then resumption of suction for another 24 hours (39). This technique has been reported to improve drainage and lung expansion in loculated empyemas as well as with loculated malignant effusions with no side effects or systemic effects on coagulation or fibrinolysis. (39,40).

Pleural Sclerotherapy

By far the most common palliative treatment of malignant pleural effusions is drainage of the pleural space with reexpansion of the lung, followed by instillation of a chemical agent into the pleural cavity. It is thought that the treatment works by causing a pleuritis designed to create a symphysis between the visceral and parietal pleurae (also called *pleurodesis by sclerotherap*) to prevent reaccumulation of fluid in this space. The most commonly used method to drain the effusion is with a chest tube, as previously described (see the section Tube Thoracostomy), and at least some nonrandomized studies suggest that this method gives superior results with sclerotherapy compared with drainage and sclerotherapy by needle thoracentesis alone (34).

Another apparent determinant of the success in pleural sclerosis is the glucose level and the pH of the pleural effusion. Several authors have found that a low glucose level (<60 mg/dl) and pH (<7.20) in the malignant effusion result in a higher recurrence rate after attempted chemical pleurodesis as well as an overall shortened patient survival (41,42). Although interesting, the exact significance of these isolated reports is uncertain and probably should not influence the choice of agent or techniques employed.

Controversy abounds as to which is the most effective chemical sclerosing agent for malignant pleural effusions. Comparison of the many published reports about various agents is often difficult because of the difference in reporting response rates, patient criteria, side effects, methods of evaluating results, and followup. The most widely followed set of guidelines to analyze results in the literature is that published by Hausheer and Yarbro (3), which is summarized in Table 28-4. However, we believe that a simpler and more accurate means of assessing therapeutic efficacy is to follow the time to recurrence compared with the chest radiograph taken after pleurodesis and removal of the chest tube. In many instances, the pleural effusion recurs or progresses, but retreatment is not indicated because the patient has progressive disease elsewhere. For assessment of therapeutic efficacy, these cases still need to be counted as “failures.” On the other hand, whether the progression is clinically meaningful—that is, needs retreatment—is a significant issue in cost-effectiveness studies.

Patient must survive 1 mo after the procedure[b]
Objective response:
No major fluid reaccumulation 1 mo after pleural sclerosis, as determined by chest radiographs
No clinical requirement for thoracentesis within that mo
Failure:
Reaccumulation of more than 50% of the original effusion volume in comparison with the immediate postpleurodesis chest radiograph
Clinical requirement for thoracentesis within 1 mo of the pleurodesis

Adapted from Hausheer FH, Yarbro JW. Diagnosis and treatment of malignant pleural effusion. *Semin Oncol* 1985;12:54–75, with permission. However, we favor a simpler evaluation using time to progression. See text for discussion.
[b]From Hausheer FH, Yarbro JW. Diagnosis and treatment of malignant pleural effusion. *Semin Oncol* 1985;12:54–75; and Austin EH, Flye MW. The treatment of recurrent malignant pleural effusion. *Ann Thorac Surg* 1979;28:196–203, with permission.
[c]From Welch JC, Kiely JM, Harrison EG Jr, et al. Pleural effusion in lymphoma. *Cancer* 1971;31:848–853, with permission.

TABLE 28-4. COMMONLY USED GUIDELINES FOR EVALUATING THE THERAPEUTIC EFFICACY OF PLEURAL SCLEROSIS[a]

Mechanism of Sclerosis

The mechanism of action of sclerosing agents appears to vary somewhat depending on the type of agent and the laboratory model tested. One of the earliest studies (43) employed the rabbit as the test animal and found that the pH of the solution instilled into the pleural cavity appeared to be an important determinant of success. The most acidic solutions tested, including unbuffered tetracycline (the most acid being pH 2.5), were quite effective in creating a small polymorphonuclear-predominant effusion and resulted in complete pleural symphysis on postmortem examination of the animals. Other agents with higher, more neutral pHs, such as nitrogen mustard and quinacrine, had no significant effect on the rabbit pleurae in this study. However, a later study by the same group (44) using the same model but adding bleomycin and sodium hydroxide to the series test agents found that the pleural sclerosing effect was actually Patient must survive 1 mo after the procedure independent of pH and was more related to the increasing dosage of tetracycline, the only agent causing a pleural sclerosis in this model.

Another rabbit study explored the effects of various dosages of intracavitary bleomycin versus tetracycline and found similar results of vigorous pleural fibrosis and symphysis with tetracycline, but no effect was seen with bleomycin (45). Minocycline was compared with tetracycline in another study using the rabbit model, and it proved to be as effective as tetracycline in creating a pleurodesis (46). When the mechanical agent talc was instilled by open thoracotomy in a study comparing various methods of pleurodesis using the canine model, this substance was found to cause a very intense pleuritis and a dense pleural symphysis that was even more pronounced than that caused by mechanical abrasion of the pleura or by tetracycline (47).

Clinical studies in humans have shown a significant discrepancy and lack of correlation with animal studies in the efficacy of sclerosing agents such as bleomycin. Bleomycin and even nitrogen mustard have been demonstrated to be highly effective agents in humans (3) despite the complete lack of effect in the rabbit model. Traditionally, it has been held that the rabbit model is of little relevance because of these discrepancies. It is possible that we are examining the wrong outcome measure. The presence or absence of pleural fibrosis [and all of its molecular findings such as a marked rise in basic fibroblast growth factor after talc pleurodesis (21)] may in fact be an epi-phenomenon. If the full role of VEGF and related compounds is better elucidated, it may well be that the balance of permeability enhancing and suppressing factors caused by variations in tumor, inflammatory response, and “sclerosing” agent is, in fact, the key determinant in measuring the outcome of various clinical interventions. The various “sclerosing” agents and laboratory measures (e.g., pH, white blood cell count) will then need to be reassessed.

Technique of Pleural Sclerotherapy

The most common technique used to instill the sclerosing agent into the pleural cavity has developed primarily from convention and common usage (3,48,49 and 50) and not on the basis of rigorous studies. After complete drainage of the pleural cavity with a chest tube and reexpansion of the lung on suction, the tube is clamped and the patient is placed into the lateral decubitus position with the affected hemithorax upward to assure that all of the sclerosing agent initially drains into the chest. Most

clinicians will administer a parenteral narcotic, such as morphine 3–6 mg, intravenously 10 minutes before the procedure to minimize the potential and unpredictable pain of the chosen sclerosing agent. Approximately 150 mg lidocaine (15 ml of a 1% solution without epinephrine) are instilled initially into the pleural cavity through the chest tube using a Luer-lock syringe and 22-gauge needle. It is allowed to dwell several minutes for local analgesia. The sclerosing agent dissolved in 50–100 ml 0.9% saline is then injected into the chest tube, and the tube is left clamped for 2 hours. The use of talc slurry requires a slightly different technique using a bulb syringe and a saline flush (51).

Usually the patient is then turned and repositioned every 15 minutes for the 2 hours to assure even distribution of the agent throughout the pleural cavity. However, when this patient repositioning maneuver was investigated carefully in a comparative clinical study, rotation of the patient during the time the chest tube was clamped offered no significant benefit to the success of the attempted pleurodesis (50). After 2 hours, the chest tube is unclamped and the tube is placed back on suction. The patient is followed with daily chest radiographs to verify continued complete drainage of the pleural cavity. The chest tube is removed when the daily drainage drops to 100 ml or less (49) (or <50 ml/8hr), and the patient is discharged the same day, once a confirmatory radiograph has been taken after removal of the chest tube. Most physicians create a moderately long subcutaneous tunnel (1.0–1.5 interspaces) through which the chest tube is initially inserted, so that with tube removal the wound seals well without the necessity (and discomfort) of placing sutures to close the skin wound.

Sclerosing Agents

Historically, a wide variety of agents have been instilled into the pleural space to create a pleurodesis (3,39,47). Table 28-5 lists most of the agents that have been described in the literature. These agents have differed greatly as to their effectiveness, side effects, availability, and even cost. Many are of only historical interest, while others, such as talc, bleomycin, and doxycycline, are in common use. Table 28-6 summarizes the efficacy of the most widely used sclerosing agents reported in the literature, comparing them with other methods of therapy designed to prevent the recurrence of malignant pleural effusions. Whenever possible, response rates are compared according to the criteria listed in Table 28-4.

Tetracycline
Doxycycline
Minocycline
Bleomycin
Talc
Quinacrine
Nitrogen mustard
Doxorubicin
Radioisotopes (I-131, Y-90, P-32, AU-198)
Mitoxantrone
Corynebacterium parvum
Bacille Calmette-Guérin cell wall skeleton
OK432 (streptococcal preparation)
Silver nitrate
Eosinophil colony-stimulating factor
Interleukin-2
Thio-TEPA
5-fluorouracil
Autologous blood
Cisplatin
Cytarabine
Mechlorethamine
Pirarubicin
Carboplatin
Mustine
Mepacrine
α, β, or γ interferon

I-131, iodine-131; Y-90, yttrium-90; P-32, phosphorus-32; AU-198, gold-198.

TABLE 28-5. INTRAPLEURAL SCLEROSING AGENTS

Technique	Response rates (%)	
	Range	Mean
Tube thoracostomy alone	0–86	22
Tube thoracostomy drainage plus	—	—
Talc	72–100	96
Bleomycin	63–85	84
Tetracycline[a]	25–100	72
Doxycycline[b]	73–95	84
Nitrogen mustard	27–95	44
Quinacrine	64–100	86
5-FU/Thio-TEPA	14–80	30
Doxorubicin[c]	18–24	24
Radioisotopes (AU-198, P-32, Y-90)	25–89	59
External radiation	—	—
Lymphoma	88–100	94
Other tumors	29–43	33
Thoracoscopy with talc poudrage[d]	87–95	92
Pleurectomy	88–100	98

AU-198, gold-198; P-32, phosphorus-32; Y-90, yttrium-90.
[a]No longer clinically available after mid-1991; replaced with doxycycline or minocycline.
[b]References 30, 44–47.
[c]References 32, 48–51.
From Hausheer FH, Yarbro JW. Diagnosis and treatment of malignant pleural effusion. Semin Oncol 1985;12:64–75, with permission.

TABLE 28-6. MALIGNANT PLEURAL EFFUSIONS: RESPONSE RATES OF CURRENTLY AVAILABLE THERAPY

Tetracycline. Since the first description of tetracycline as an agent for intrapleural sclerotherapy in 1972 by Rubinson and Bolooki (52), this agent has gained widespread acceptance and was preferred in the United States (53) and Europe (54). The intrapleural dosage of 500 mg was initially used, but soon, as clinical studies began to appear, the standard dose became 1 g (20). This agent has demonstrated consistent efficacy, with a mean objective response (using the increased 1-g dose) of 69–85%, averaging 72% (3,48). It has been proved to be safe, effective, quite inexpensive, and easily administered, with adverse reactions limited to fever (7–33%) and pain (17–62%) (3,30). The effect of tetracycline was generally believed to be related to its low pH of 2.0–3.5, which caused an extensive pleuritis in the rabbit model. However, a hydrochloric acid solution of the same pH failed to achieve the same sclerosing effect, which suggests that tetracycline had other actions (43). Unfortunately, parenteral tetracycline is no longer commercially available.

Over the years, a variety of comparative clinical series, mostly nonrandomized, have been published with disparate methodology, patient selection, and response criteria, as well as retrospective analyses and variable results (3,48). Despite these limitations, most older studies comparing tetracycline with other agents such as nitrogen mustard, quinacrine, mustine, doxorubicin, bleomycin, and *Corynebacterium parvum* consistently demonstrated that tetracycline gave superior or at least equivalent results with much less toxicity (55). Of the few recent randomized larger trials, the series of Ruckdeschel and associates (56) and Johnson and Curzon (57) comparing intrapleural bleomycin and tetracycline showed a significantly better response to pleurodesis with bleomycin, with similar toxicity profiles. Nevertheless, tetracycline's ready availability and lower cost kept it as a preferred agent for pleurodesis of malignant effusions (53,54).

Doxycycline. Clinical studies with doxycycline have begun to accumulate now, after the demise of parenteral tetracycline (58), but all thus far have been nonrandomized, noncomparative trials (39,59,60 and 61). Despite these limitations, doxycycline has consistently demonstrated effective results: response rates range from 73–95%, which is similar to those of bleomycin (Table 28-6); yet, its toxicity is also similar, and its pain on administration may actually be less than tetracycline. The 500-mg dosage of doxycycline empirically chosen for these preliminary studies was probably too low, since over one-third of patients required repeat dosing to be effective (39). The major problem in using doxycycline, as noted in prior studies, is that it frequently requires several dosings to obtain equal efficacy (62), and this seriously reduces its cost effectiveness because of the need for longer hospitalizations (63).

Minocycline. Minocycline has had much less use for pleural sclerotherapy. Rabbit studies (46,62) demonstrate inflammatory changes in the pleura similar to those seen with tetracycline. The only clinical series reported using minocycline (300 mg) was small, with seven patients, but the complete response rate was 86%, similar to that of doxycycline, and the reported toxicity was likewise low (64). However, little information is currently available on this agent, and its eventual role in pleural sclerotherapy awaits further study.

Bleomycin. The most extensively studied cytotoxic chemotherapeutic agent used for intrapleural sclerotherapy is bleomycin. Not only does it play a significant role in the treatment of various solid tumors by parenteral administration, but also it has been shown to be highly effective in the palliative treatment of malignant pleural effusions, with response rates averaging 84% (3). Numerous nonrandomized studies have compared this agent to its primary competitor tetracycline, and most have suggested that there is no significant difference in efficacy or toxicity (55).

A few randomized trials of bleomycin versus tetracycline have been performed, with varying results. Kessinger and Wigton (65), in their study of 41 patients, found no significant difference in the response rates using 89 units of bleomycin (67%) versus 500 mg tetracycline (61%), and both agents had similar toxicities. However, Ruckdeschel and associates (56), in their multiinstitutional randomized study of 74 patients receiving either 60 units bleomycin or 1 g tetracycline intrapleurally, found the complete response rate at 1 month to be 64% (18/28) in the bleomycin arm and 33% (9/27) in the tetracycline arm. Unfortunately, not all patients in this trial were restudied at 30 days, although the complete response rates were also significantly different at 90 days with 70% (26/37) and 47% (17/36), respectively. Johnson and Curzon, in their randomized trial of 60 patients, found an 87% complete response rate at 90 days with bleomycin, compared with 56% with tetracycline (57). The acute toxicities of both drugs were similar, although there tended to be a higher incidence of pain in the tetracycline arm in both of the latter studies (56,57) (Table 28-7).

Time to recurrence of the effusion
Necessity for further treatment of recurrent effusions
Extent of postinstillation complications
Duration of chest catheter following pleurodesis
Duration of hospitalization if retreatment is needed for recurrent effusion
Survival

ECOG, Eastern Cooperative Oncology Group.
From Matsuzaki Y, Shibata K, Yoshioka M, et al. Intrapleural perfusion hyperthermo-chemotherapy for malignant pleural dissemination and effusion. *Ann Thorac Surg* 1995;59:127–131, with permission.

TABLE 28-7. MULTI-INSTITUTIONAL PROSPECTIVE, RANDOMIZED TRIAL (ECOG 8592) COMPARING INTRAPLEURAL BLEOMYCIN VERSUS DOXYCYCLINE VERSUS TALC: ENDPOINTS TO MEASURE

Although 45% of the intrapleural dose of bleomycin is absorbed (66), myelosuppression is not seen. However, since the plasma half-life of bleomycin increases with renal failure, systemic toxicity with alopecia and mucositis is possible and has rarely been reported in renal failure patients (67). Therefore, caution is advised in using intrapleural bleomycin in patients with renal failure. Some have also recommended using the lower dose of 40 units/m^2 body surface area in the elderly because of their potential reduced plasma clearance of the drug (68).

The major disadvantage of bleomycin is its elevated cost in comparison with other agents such as doxycycline and talc. This has been the major impediment to its widespread use. However, if it proves to be a more effective agent resulting in reduced hospital stays, and if consistently only a single dose is required for sclerotherapy, the cost factor may be overcome and bleomycin may actually be less expensive overall. And it is important to remember that one additional hospital day would pay for any extra cost of this agent, if it is actually more efficient than less expensive agents.

D. K. Fuller (69) and Belani and associates (63) argue that bleomycin is more cost effective overall than talc, tetracycline, and doxycycline on the basis of their questionable post hoc comparative analyses of a variety of disparate clinical studies (often published many years apart) that commonly used inadequate doses of the test agent in the trials (i.e., 500 mg doxycycline instead of the current 1 g).

Talc

Talc Insufflation. Talc is a generic term referring to a natural product containing the mineral talc (a trilayered magnesium sheet silicate) found in talcose or soapstone, which is usually contaminated with chlorite and trace minerals (quartz, calcite, and dolomite) (70,71) The most important contaminant of talc is asbestos (fibers of actinolyte, amosite, anthophyllite, chrysolite, crocidolite, and tremolite), which has been linked to carcinogenesis. However, for clinical use, USP talc has been purified with particle sizes generally less than 50 µm. Most important, USP talc has been asbestos-free for many years, although it still requires sterilization prior to use.

Talc is the oldest, cheapest to purchase, and perhaps the most effective agent in causing a pleurodesis. The first description of talc as a pleural sclerosant was in 1935 by a Canadian surgeon, Norman Bethune, who insufflated talc into the pleural cavity of dogs and cats after creating a pneumothorax (72). Two patients were also described receiving an intrapleural dusting of talc just prior to lobectomy to create adhesions. Multiple studies with various animal models have followed, with the most recent by Mathlouthi and associates (73) demonstrating that talc insufflated into dogs causes a nondose-dependent parietal and visceral inflammation followed by a granulomatous pleural reaction. After talc administration, the resultant intense adhesive pleuritis, possibly accompanied by an adhesion-stimulating factor (70) obliterating the pleural space, is believed to be its primary clinical benefit in preventing the recurrence of malignant pleural effusions (71).

Insufflation of talc into the pleural cavity, or talc poudrage (“powdering”), is highly effective. Many studies demonstrate a response rate with malignant pleural effusions ranging from 87–95%, averaging 92% (41,70,71,74). The successful use of talc insufflation has also been described with benign effusions, chylothorax, pneumothorax, and even empyema (70). The primary disadvantage of talc poudrage is the requirement for thoracoscopy to be performed, usually with the patient under general anesthesia, to allow complete collapse of the lung to assure uniform distribution of the talc. An atomizer or bulb syringe is filled with dry talc, usually 2.5–5.0 g, and the talc is blown into the the pleural cavity after ensuring that all loculations are removed. In selected patients, the risks of this procedure are small, with low perioperative morbidity and mortality (70). However, many patients with malignant pleural effusions are debilitated and are poor candidates for an operative approach, or they are reluctant to have such a procedure because of their short life expectancy. In addition, thoracoscopic talc poudrage usually increases hospitalization time, adds surgical and anesthesia costs, and increases the potential for complications. Fortunately, several studies have suggested that similar results are possible with bedside talc slurry administration through a chest tube, obviating the need for the more invasive operative approach (3,51).

Currently, there is an ongoing national cooperative randomized trial of sclerosis of pleural effusions with intrapleural talc comparing delivery by videothoracoscopic insufflation with delivery by chest tube instillation as talc slurry (Cancer and Leukemia Group B 9334). The results of this study should answer the question which is the preferable technique in terms of efficacy and cost effectiveness.

Talc Slurry. Twenty-three years after the first described use of talc with an open thoracotomy, J. S. Chambers in 1958 reported the successful use of talc instilled through a tube thoracostomy to control a malignant pleural effusion (75). In subsequent studies (48,51,70,55,76), the administration of talc in a suspension or slurry has proved to be as efficacious as by poudrage (62,71), with response rates ranging from 72–100% and averaging 96% (3). The administration of talc slurry is generally performed at the bedside with 2–5g of sterile USP talc suspended in 30–50 ml 0.9% saline solution in a bulb syringe instilled into a larger-bore chest tube after complete drainage of the pleural space. Usually, intrapleural lidocaine premedication is used (51,70).

Although the efficacy of talc is generally well recognized, concerns about its adverse effects and safety have slowed its use. The usual side effects reported are pain on administration in most patients (51), but this is readily manageable, as with other sclerosing agents. Fever also accompanies talc slurry administration 16–69% of the time, but it is usually short-lived (71). Talc empyema is reported in 0–11% of cases (71) and can be exceedingly difficult to treat effectively, because talc is a foreign body and cannot be removed from the site of infection: the pleural cavity. Nevertheless, in at least one series talc has actually been instilled to obliterate the pleural space after empyema (70).

However, the more worrisome potential adverse effects are rare but definitely can occur, including talc microemboli to the brain (71); pulmonary complications of acute pneumonitis, pulmonary edema, and adult respiratory distress syndrome (78); and death (62,71). The definite mechanism of respiratory complications is unknown. But it is probably related to the suspected uptake of talc by the parietal pleural lymphatic system, with subsequent transport to the mediastinal lymph nodes and thoracic duct and hence to the systemic circulation (78,79). Talc administration has been reported (71) to be associated with a variety of acute cardiovascular complications—arrhythmias, cardiac arrest, chest pain, myocardial infarction, and hypotension—but it is often difficult to attribute these effects to the talc itself versus the other coexisting procedures, such as thoracoscopy in some cases. Preliminary results of Cancer and Leukemia Group B 9334 were reported at the 2000 American Society of Clinical Oncology meeting. There was little difference in clinical outcome between talc poudrage or talc slurry but both treatments caused a nontrivial incidence of significant respiratory distress (15–16%) and death (6.5%) (80).

The last hurdle to the use of talc is the need for sterilization at the point of use, because it has yet to be readily available as a sterile preparation in the United States. Ethylene oxide gas, gamma irradiation, and dry heat sterilization, along with surveillance cultures of each batch of sterilized talc, are methods that have been described, although no one method is considered standard (81). Of these techniques, dry heat sterilization is the least expensive and the most commonly used. A commercially produced disposable spray canister of 4 g of asbestos-free talc for use during talc poudrage has recently been described (82), although its availability in the United States has been sporadic and is currently unreliable. Whether talc should be employed in this clearly palliative setting has engendered a significant amount of controversy (85).

Other Antineoplastic Agents

One of the first agents used intrapleurally to treat malignant effusions was the cytotoxic agent nitrogen mustard. This alkylating agent is highly reactive and loses its activity within minutes after contact with tissue. The response rates with nitrogen mustard varied greatly in various small series, from 27–95%, but averaged only 44% (3). When it was compared with other agents, the response rates were generally lower but the adverse reactions were much higher (3). The toxicity of nitrogen mustard was severe nausea and vomiting, commonly for 24 hours, in addition to local pain and fever (48). The lack of efficacy and its significant toxicity have made this an

undesirable agent, of historical interest only (30).

Many other chemotherapeutic agents have been described in various small series, including thio-TEPA, 5-fluorouracil, doxorubicin, combination cisplatin and cytarabine, etoposide, mitoxantrone, and mitomycin-C (3,30,62). Generally, the results have been unimpressive and clearly are no better than those obtained with more common agents such as tetracycline and its derivatives or bleomycin (3). However, their systemic absorption by intrapleural administration is considerable and often leads to prolonged plasma levels and significant systemic toxicity, including myelosuppression. At present, the use of these agents in this context is investigational and is not generally recommended (10,30,62).

Biological Agents

Corynebacterium parvum

Corynebacterium parvum is an anaerobic gram-positive bacterium first described for intrapleural use to cause a pleurodesis in a trial in six patients in 1978 (82). Its effect was not found to be from its postulated role as stimulator of cell-mediated immunity. Rather, C. *parvum* recruits neutrophils to the pleura, causing a subsequent fibrogenic response with fibrotic pleural thickening (83). C. *parvum* averaged response rates of 76% in single-agent studies but consistently demonstrated the same or worse response compared with bleomycin or tetracycline (49,62). C. *parvum* also has moderate toxicity, including fever (5%), pain (43%), cough (6%), and nausea (39%), and furthermore requires multiple instillations over a 2-day period. C. *parvum* offers no advantages as a pleural sclerosant and is also not available in the United States, resulting in its lack of current clinical use.

Interferons and Interleukins

The most recent attempt to use biological therapy for malignant pleural effusions involves the use of interferon-a, b, or g with the intent to stimulate natural killer cells, in addition to their cytotoxic effects (62). The response rates have not been impressive, with only a 41% complete response in a series of 29 patients (84). Intrapleural administration of interferon still remains investigational.

Several recent studies have investigated the use of recombinant interleukin-2 alone or in combination with lymphokine-activated killer cells in malignant pleural effusions from lung cancer (86,87). These preliminary studies have commonly shown the disappearance of the pleural effusion and occasionally the cancer cells themselves (87), but no serious side effects occurred. These studies are intriguing but require more study in larger patient groups.

Radioactive Isotopes

Finally, the use of intrapleural radioisotopes, especially radioactive gold and phosphorus, for control of malignant pleural effusions had a period of popularity beginning in 1951 when they were first described (88) until the late 1960s. The overall effectiveness of these agents was less than that of other available agents, with a mean response rate of 59% (3). The isotopes were also expensive and potentially hazardous to hospital personnel, patients needed to be isolated until the radioactive emissions were acceptably low, and special personnel and equipment were needed. Because of their relative ineffectiveness and their many disadvantages, radioisotopes are not currently recommended for pleural sclerotherapy and are of historical interest only (3).

Surgical Interventions

Pleurectomy

A thoracotomy with mechanical pleurodesis, or a pleurectomy to remove most of the parietal pleura, has occasionally been done in the past as a primary procedure for malignant effusions. Martini and associates (89) in 1975 reported the use of pleurectomy in 106 patients with malignant effusion and saw no recurrence in 100%, but there was a 9% mortality and a 23% rate of major complications: bleeding, air leaks, pneumonia, empyema, pulmonary embolus, respiratory insufficiency, and cardiac failure. Currently, this procedure should be considered for application only at the time of thoracotomy when a lung cancer is found to be unresectable with pleural metastases. Occasionally, a well-selected patient of good performance status and a long life expectancy, in whom all other attempts at control of the effusion have failed, might be considered a candidate for open pleurectomy. However, the advent of videothoracoscopy now allows these procedures to be done, if necessary, in a minimally invasive manner, essentially making an open thoracotomy for this purpose rarely necessary.

Pleuroperitoneal Shunt

Internal drainage of the malignant effusion into the abdomen using an implanted, valved, manually operated pump (Denver shunt, Denver Biomaterials; Denver, CO) was initially described in 1984, with the most recent series reported in 1993 (90). Implantation of this device usually requires general anesthesia (local anesthesia occasionally may be used in selected patients) and the performance of a small thoracotomy and small celiotomy that are needed to implant the two limbs; the pump is implanted subcutaneously. Since the shunt must carry fluid from a negativepressure area (the pleural cavity) to a positive-pressure area (the abdomen), major patient or family participation is necessary. For the shunt to function properly, it requires manual pumping 100 times on five occasions per day. The shunt is occasionally an option in compliant, wellmotivated patients with good performance status who have a trapped lung and an intractable effusion (5,10,49). Malfunction of the shunt over time, requiring its replacement, may further limit the usefulness of this device.

Videothoracoscopy

As experience with VATS grows, some investigators are now reporting series of successful VATS pleurectomy for malignant effusions. Waller and associates (91) performed a VATS parietal pleurectomy on 19 patients (13 mesothelioma and 6 metastatic adenocarcinoma) with no operative deaths or major complications, and the median hospital discharge was on the fifth day. Another approach to VATS pleurectomy was described by Harvey and colleagues (92) in 11 selected patients with malignant pleural effusion in which they performed a parietal pleurectomy assisted by dissection of the pleura with a stream of water (hydrodissection). The effusion did not recur in any patient.

Another Invasive Technique

An innovative technique for approaching the lung cancer patient with pleural metastasis was described recently by Matsuzaki and associates (93). This approach took advantage of the antineoplastic effect of hyperthermia. The pleural cavity was irrigated using an extracorporeal circuit with a 43°C saline and cis-platinum solution for 2 hours in 12 patients with pleural metastases, who also underwent resection of their primary tumors. The pleural effusion was controlled in all 12 patients, and their median survival was 20 months, compared with 6 months in a cohort of seven matched control patients with pleural metastases. This report is preliminary but provocative, and the technique bears watching as further work is reported.

Recurrent Effusions

The most perplexing and frustrating problem to deal with is the refractory pleural effusion in which the first attempt at pleural sclerotherapy failed. Generally, a second attempt at tube thoracostomy followed by intrapleural sclerotherapy is recommended, usually employing a different agent. If this second attempt fails, and if the patient has a good performance status and a reasonable estimated life span, then proceeding with VATS talc poudrage or VATS pleurectomy may be an option. Alternatively, such a patient may rarely be a candidate for a pleuroperitoneal shunt.

Recommendations

It is important to remember that the primary goal of therapy of a malignant pleural effusion is entirely palliative. The patient generally has a terminal disease with a very limited life span, usually counted in terms of a few months at best. The choice to treat and the actual treatment chosen must reflect the clinician's realistic understanding of the patient's overall prognosis and a desire to provide these terminally ill patients with the maximum possible comfortable time at home with the best quality of life. The timing of treatment is also critical. Waiting for “significant” symptoms to develop before draining a malignant effusion rarely improves the palliative benefits for the patient.

Our recommendations are as follows:

1. In a patient with a chemosensitive tumor such as lymphoma, breast cancer, or small cell lung cancer, systemic therapy is the treatment of choice. If a thoracentesis is not needed for staging purposes, the patient can proceed directly to treatment if the effusion is asymptomatic, otherwise a therapeutic thoracentesis followed by

systemic treatment is preferred.

2. In the patient with a less responsive or refractory solid tumor, all significant effusions should be drained and treated. We prefer standard chest tube drainage at present but await comparative data on small bore catheters (94). Our choice of sclerosing agent is not clearly resolved, with bleomycin, doxycycline, and talc all having their proponents. Our first choice is for a clinical trial. Talc is used whenever a second pleurodesis needs to be done for recurrent disease. We almost never use shunts.

3. Our policy is increasingly moving to earlier use of thoracoscopy, in lieu of a second diagnostic thoracentesis. This reflects our situation as a cancer hospital and the benefits of being able to reduce adhesions, draw the fluid, and initiate drainage all at the same setting.

PERICARDIAL EFFUSIONS

Incidence

The appearance of a malignant pericardial effusion in patients with advanced cancer is not uncommon. In collected autopsy studies of patients with disseminated cancer, involvement of the heart and pericardium with metastatic malignancy is seen in up to 21% of cases (49,95,96,97 and 98), with the highest incidence occurring in patients with leukemia (69%), melanoma (64%), and lymphoma (24%) (98). Because a large number of patients with malignant pericardial effusions are asymptomatic, autopsy studies tend to have a higher incidence than in clinical series (99). In terms of the actual clinical impact of symptomatic pericardial effusions, there were 7000 patients who underwent pericardiectomy for all causes in U.S. hospitals in 1993 (100). Generally, 25–50% of all patients requiring surgical pericardial drainage have proven malignant pericardial involvement (101,102 and 103). Because not all patients with a malignant pericardial effusion undergo a pericardiectomy, the total number of patients developing this complication of advanced cancer is much higher.

Etiology

Almost any tumor (except primary tumors of the brain) can metastasize to the pericardium and lead to an effusion (99). However, the most common tumors to involve the pericardium and heart are the same as with malignant pleural effusions: tumors of the lung and breast, lymphoma, and leukemia. These metastatic tumors account for almost 75% of all pericardial malignancies (104). When it metastasizes, melanoma frequently involves the heart, occurring in up to 50% of cases (104). Other malignancies that may spread to the pericardium to cause an effusion include gastrointestinal tumors and sarcomas. Primary tumors of the pericardium can cause effusions, but they are rare and include sarcomas, malignant teratomas, and mesotheliomas. Searching for the cause of a symptomatic pericardial effusion is critically important, because approximately 40% of patients with an underlying cancer have a nonmalignant cause of the effusion (105).

Pathophysiology

The pericardium, as it is commonly known, is actually the parietal pericardium. The visceral pericardium is a monocellular serosal layer constituting what is also known as the epicardium of the heart. Together, both pericardial layers constitute a serosal sac containing at any one time 15–50 ml of low-protein fluid. The pericardium is flexible but relatively inelastic. It probably functions to mechanically protect the heart from outside friction, provide a barrier from inflammation, maintain cardiac position against gravitational forces and acceleration, and support the thinner heart chambers such as the atria and the right ventricle (105).

Like the pleurae, the fluid inside the pericardial sac is normally in a balanced steady state of secretion by the serosal surface and reabsorption by the visceral (epicardium) and parietal pericardia. The increase in pericardial fluid that may lead to tamponade generally results from obstruction of the mediastinal lymphatic system, commonly by tumors, such as lung and breast cancers, that involve the mediastinal lymph nodes. Infiltration of the epicardium by tumor may block subepicardial venous flow, resulting in an outpouring of fluid into the pericardium. The parietal pericardium may also be infiltrated by tumor, resulting in increased fluid secretion. The result of blockage of pericardial fluid reabsorption, as well as often a net increase in secretion, may ultimately result in a symptomatic pericardial effusion (106,107). The role of VEGF or other growth factors modulating vascular permeability is unknown, with no reported series to date.

When fluid increases slowly, the pericardium will distend greatly, up to as much as 2 liters, before the pericardium becomes tense. However, when the fluid accumulates more rapidly, the pericardium fails to stretch, pericardial pressure rises, and hemodynamic compromise may occur with as little an accumulation as 200 ml (108). The critical effect of this increase in pericardial pressure is impaired diastolic filling of the right side of the heart. The condition termed *cardiac tamponade* develops when there is “hemodynamically significant cardiac compression due to accumulating pericardial contents that evoke and defeat compensatory mechanisms” (109). On the basis of Starling's law, impaired diastolic filling will result in a depressed stroke volume and cardiac output. A greater volume of pericardial fluid and pressure causes an increase in ventricular diastolic pressure, which further impairs venous return, leading to a declining cardiac output. The autonomic nervous system responds to this decreased stroke volume and initially compensates by a release of catecholamines, resulting in an increased heart rate and arterial and venous vasoconstriction. The kidneys also respond to the decreased cardiac output by increasing sodium and fluid retention, leading to increased intravascular volume and venous pressure. Eventually, these compensatory mechanisms fail as intrapericardial pressure rises (often abruptly), resulting in a further decline in cardiac output with hypotension and circulatory collapse (108).

Clinical Presentation

Symptoms

Nearly two-thirds of the patients with metastatic tumor involving the heart and pericardium will have no definite cardiovascular signs or symptoms (95), even when a careful history is taken. When the initial symptoms of a malignant pericardial effusion begin, they are often subtle and may be attributed to the underlying primary tumor. The actual development of symptoms depends on the rate at which the effusion accumulates, the actual effusion volume (and how close it is to causing maximal pericardial distention), and the underlying cardiac function, which itself may be impaired because of myocardial metastases or prior chemotherapy, as with doxorubicin (104,108). When the intrapericardial pressure increases sufficiently to impair diastolic ventricular filling, then symptoms begin appearing.

The most common and earliest symptom is dyspnea on exertion (93% of symptomatic patients), which may progress to dyspnea at rest as cardiac function is progressively compromised (95,104,109). Dyspnea is also the initial presenting symptom in patients with a malignant pleural effusion, a much more common complication of advanced cancer. A pleural effusion occasionally accompanies a malignant pericardial effusion, and this by itself may draw attention away from the actual pericardial problem and confound the diagnosis. A comparison of the presenting signs and symptoms of pericardial and pleural effusions is found in Table 28-8 (94,110). Other common symptoms include chest pain or heaviness (63%), cough (30–43%), and weakness (26%) (94). Less common symptoms include peripheral edema, low-grade fever, dizziness, nausea, diaphoresis, and peripheral venous constriction. The presence of peripheral edema often leads unsuspecting clinicians to give diuretics, which significantly worsen the underlying physiological problem. Cyanosis from decreased venous return and venous hypertension, and agitation and tachypnea from low cardiac output and hypoxia, are late manifestations of pericardial tamponade (104,109).

Frequency	Pericardial	Pleural
Common	Dyspnea (exertion)	Dyspnea (exertion)
	Dyspnea (rest)	Dyspnea (rest)
	Chest pain or heaviness	Orthopnea
		Cough
	Cough	Percussion dullness
	Jugular venous distention	Egophony
		Percussion dullness
	Hypotension	—
	Pulsus paradoxus	—
	Resting tachycardia	—
Uncommon	Cyanosis	Cyanosis
	Peripheral edema	Pleuritic chest pain
	Low-grade fever	Anorexia
	Distant heart sounds	—
	Peripheral vasoconstriction	—
	Narrowed pulse pressure	—
	Kussmaul's sign	—
	Low-voltage electrocardiogram (limb leads)	—
	Electrical alternans	—
	Hepatojugular reflux	—
	Pleural effusion	—

Adapted From Buckdahl JC. Malignant effusions in the chest. In: Kirkwood JM, Logan MT, Yaska JM, eds. *Current cancer therapeutics*, 2nd ed. Philadelphia: Churchill Livingstone, 1994:304–308, with permission.

TABLE 28-8. COMPARISON OF THE PRESENTING SIGNS AND SYMPTOMS OF MALIGNANT PLEURAL AND PERICARDIAL EFFUSIONS

Signs

The classic signs associated with cardiac tamponade were described in 1937 by Claude Beck and are often referred to as *Beck's triad*: quiet heart sounds, hypotension, and venous distention (111). These signs remain the most commonly seen, although the muffled heart sounds may be more difficult to appreciate clinically. Unfortunately, all of these clinical signs appear late in the course of the physiological deterioration. Therefore, waiting for them to develop before ordering diagnostic tests is inappropriate. Hypotension is found in 41–63% of patients, elevated venous pressure is seen in 50–63%, and resting tachycardia occurs in 68–89% (95). The venous pressure is almost always elevated in cardiac tamponade, although rarely it may be normal or low if the patient is hypovolemic. A central venous pressure greater than 15 mm Hg with hypotension is highly suggestive of tamponade.

The pathophysiologic effects of cardiac tamponade tend to exaggerate the normal fall in systolic blood pressure (usually less than 10 mm Hg) and stroke volume that occur with inspiration. The causes of this normal event are controversial but are thought to involve any or all of the following: (a) inspiratory pooling of blood in the lungs with decreased filling of the left side of the heart, (b) increased right ventricular filling with leftward movement of the interventricular septum to cause reduced left ventricular filling and increased afterload, (c) a fall in left ventricular stroke volume as a result of increased left ventricular transmural pressure, and (d) “reverse thoracic pump” mechanism that is due to an inspiratory decrease of intracavitary left ventricular pressure relative to atmospheric pressure (109). Cardiac tamponade exaggerates this normal physiology and was termed by Kussmaul in 1873 to be a *pulsus paradoxus*. This term is a misnomer, because it refers to the accentuation of a normal phenomenon, not a reversal of it. Clinically, a patient is considered to have a pulsus paradoxus if the inspiratory drop in the systolic blood pressure is greater than 10 mm Hg. Although strongly associated with tamponade, a pulsus paradoxus may also be detected in other conditions such as pulmonary embolism, chronic obstructive lung disease, obesity, failure of the right side of the heart, and tense ascites.

Other signs, less frequent, that may be present include a narrowed pulse pressure, a visible increase in venous pressure on inspiration (Kussmaul's sign), hepatomegaly, hepatojugular reflux, peripheral edema, cyanosis, pericardial friction rub, arrhythmias, cold clammy extremities, lowgrade fever, and ascites.

Diagnosis

Radiographic

In a patient with cancer with or without symptoms, a change in the size and contour of the heart with clear lung fields on a standard chest radiograph should alert the clinician to consider the diagnosis of a pericardial effusion. The cardiac silhouette may resemble the so-called “water-bottle heart” with bulging of the normal contours. Nevertheless, a normal-size heart shadow does not exclude the presence of a pericardial effusion or even a life-threatening tamponade. A coexisting pleural effusion may be present in up to 70% of patients with pericardial effusion (95).

Chest CT obtained for staging or followup in a cancer patient will reveal a pericardial effusion with more sensitivity than a standard chest radiograph (95). The chest CT scan may suggest a malignant pericardial process if the effusion has a high density, there is pericardial thickening, masses are contiguous with the pericardium, or there is an obliteration of the tissue planes between the mass and the heart. As a screening tool, however, chest CT has limited usefulness because of the blurring of the pericardial contents on the scan caused by continuous cardiac motion.

Another more invasive diagnostic procedure is catheterization of the right side of the heart, which can easily be done at the bedside in the intensive care unit. The passage of a flowdirected pulmonary artery catheter (Swan-Ganz catheter; Edward Lifesciences, Irvine, CA) is a common critical care procedure that can establish the presence of a cardiac tamponade. The findings from this procedure in true tamponade are depressed cardiac output and the equalization of diastolic pressures in all heart chambers (109). Specifically, the right atrial mean, the right ventricular diastolic, and the pulmonary capillary wedge pressures all tend to equalize in tamponade and can be readily measured with the pulmonary artery catheter. However, if malignant pericardial effusion is suspected, catheterization of the right side of the heart is rarely necessary, because echocardiography is sensitive enough to establish a reliable diagnosis of tamponade noninvasively, thereby allowing for prompt pericardial decompression.

Electrocardiography

The electrocardiogram often has changes associated with a pericardial effusion, including tachycardia, atrial and ventricular arrhythmias, low-voltage QRS, and diffuse nonspecific ST and T wave abnormalities. Electrical alternans is occasionally seen and consists of alternating large and small P wave and QRS complexes, caused by the increased rotary motion of the heart in the large fluid-filled pericardium. This interesting electrocardiographic abnormality generally resolves immediately with drainage of the effusion (96,109).

Echocardiography

The most sensitive and precise tool used to evaluate a peri-cardial effusion is echocardiography, usually in the two-dimensional mode (95). Any patient suspected of having an effusion deserves to have an echocardiogram. Not only is this examination rapid and noninvasive, it can be per-formed quickly at the patient's bedside even with the patient in a sitting position, and this instrument is then available immediately to aid in the performance of a diag-nostic or therapeutic pericardiocentesis. Echocardiography is extremely sensitive and may detect as little as 15 ml of fluid, as well as identifying myocardial masses and even loc-ulations of fluid.

Aside from its role in the diagnosis of a pericardial effu-sion, echocardiography is quite useful in assessing the hemodynamic consequences of the effusion. Cardiac tamponade is suggested by diastolic collapse of the right atrium or ventricle, inspiratory decrease in left ventricular dimen-sions, inspiratory increase in right ventricular dimensions, or failure of the inferior vena cava to collapse on inspiration (inferior vena cava plethora) (112,113). Prompt perfor-mance of an echocardiogram in a patient with a suspected effusion is quite important, since only 69% of patients with echocardiographic signs of tamponade are suspected of having a tamponade clinically prior to the study (114).

The most powerful predictor of the development of subsequent cardiac tamponade is the size of the effusion, because not all effusions will lead to hemodynamic compromise (115). Although the ready availability of echocardiography has allowed the earlier diagnosis of effusions in more patients, it also may have led to some overdiagnoses (116). Small effusions without symptoms are very rarely malignant and almost never require invasive evaluation or treatment. In addition, it is most uncommon for isolated pericardial disease to be the initial manifestation of new malignant disease (116).

Pericardial Fluid Examination

Percutaneous, ultrasound-guided pericardiocentesis can safely be performed in patients with larger effusions (>1 cm anterior clear space on echocardiogram). It will yield pericardial fluid for examination in approximately 90% of patients and will promptly and temporarily relieve tamponade (95,114). The fluid obtained should be sent to the lab for cytology and for determination of LDH and total protein levels. If the patient has symptoms suggesting an infectious or rheumatologic cause of the effusion, other tests, such as glucose, cell count, and culture, should be added. This is rarely needed in the patient with an obvious intrathoracic malignancy. In a malignant pericardial effusion, the result of cytology will be positive for malignant cells in 65–90% of cases (49,99,109,117,118). False-negative cytologic results are frequently seen with lymphoma and mesothelioma. However, the lack of malignant cells in the effusion fluid obviously does not exclude the possibility of neoplastic pericarditis, and it is often necessary to obtain pericardial tissue for histology if a malignant diagnosis is still suspected.

Bloody (“crank-case oil” appearance) or serosanguineous fluid is associated with neoplastic pericarditis, but it may also be seen with idiopathic causes. Malignant effusions are bloody or serosanguineous in 76% of cases and serous in the rest (119). This bloody fluid never clots because it is defibrinated by the motion of the heart inside the pericardium in addition to the intrinsic, local fibrinolytic activity of the serosal lining of the pericardium (106).

Differential Diagnosis

Because up to 40% of patients with a symptomatic pericardial effusion and an underlying cancer will have a benign cause of the effusion and perhaps require different treatment, it is important to find out the specific cause of the effusion (105). Of particular importance in the differential diagnosis is radiation-related pericardial effusion in patients who have received mediastinal radiation therapy (especially >4000 cGy) (121). From 7–30% of these patients may develop effusive or effusive-constrictive pericardial disease, usually within 24–36 months (occasionally within just a few weeks) of the radiotherapy (105,121). Purulent or tuberculous pericarditis is another possibility to consider, especially in the cancer patient who is debilitated and febrile. Drug-induced pericarditis from agents, such as procainamide or hydralazine, or even from cancer chemotherapy drugs, such as doxorubicin (pericarditis-myocarditis syndrome) (122) may occasionally occur. Idiopathic (viral), uremic, hypothyroid, cholesterol, postmyocardial infarction, or autoimmune pericarditis are other considerations in the differential diagnosis (99). Generally, the pericardial fluid analysis plus the patient's history will exclude most of the potential diagnoses and will pinpoint the actual cause of the effusion. In patients with cancer and evidence of a significant effusion of echocardiogram, we do not perform an intervening pericardiocentesis, but perform fluid analysis on the fluid removed at the time of treatment.

Prognosis

Although cancer patients with cardiac tamponade from a malignant pericardial effusion usually are severely ill at presentation, prompt relief of the tamponade will often allow them to return to a surprisingly good functional status for significant time intervals. The quality and quantity of life depends largely on the histology of the malignancy and its extent. After surgical drainage of the pericardial effusion, breast cancer patients have a mean survival of 8–18 months (102,116,118,123); lymphoma patients have a mean survival of 10 months (123). Lung cancer patients fare somewhat worse, with a mean 3–5-month survival (102,123). However, the extended survival of these advanced cancer patients with malignant pericardial effusions underscores the importance of tailoring treatment of this complication to provide maximal benefit with the least chance of reaccumulation of the effusion.

Treatment

The optimal therapy for this problem is controversial. The medical literature is filled with reports about various therapeutic options (Table 28-9) whose results vary as widely as the techniques. When these invasive techniques are compared, it is important to focus on the most recent reports, because the associated morbidity and mortality as well as the results generally improve with further experience. In the discussion that follows, each option in therapy will be discussed, but true comparative data among techniques are not currently available.

Pericardiocentesis with or without catheter drainage
Intrapericardial sclerosis with chemicals or radioisotopes
Chemotherapy
Radiotherapy
Subxiphoid pericardiectomy ("window")
Left anterior thoracotomy with pericardiectomy
Median sternotomy with pericardiectomy
Videothoracoscopic pericardiectomy
Pericardioperitoneal shunt
Percutaneous balloon pericardiotomy

TABLE 28-9. TREATMENT OPTIONS WITH MALIGNANT PERICARDIAL EFFUSIONS

Pericardiocentesis

The earliest described method of nonsurgical drainage of the pericardium, performed by Schuh in 1840, was pericardiocentesis, which he used to relieve a hemorrhagic effusion in 30 patients, of whom seven subsequently survived (124). As techniques have evolved and safety has improved, pericardiocentesis has remained the most common approach for diagnosis and therapy in patients with malignant pericardial effusions (119). It may be performed quickly under local anesthesia and is the initial procedure of choice in the emergency management of life-threatening tamponade (119).

Pericardiocentesis is best performed from the subxiphoid approach, with the needle inserted between the xiphoid and the left costal arch at a 45 degree angle directed toward the left shoulder. This is the easiest and safest approach because there is a smaller chance of damaging a coronary artery. The patient is placed in the semi-Fowler's position so that most of the effusion is in the most dependent portion of the pericardium inferiorly (125). In a true emergency, the needle can be advanced blindly or with electrocardiographic monitoring with the needle attached to a V lead. With continuous electrocardiographic monitoring, contact with the epicardium will be seen as an immediate ST segment elevation, often with premature ventricular contractions, warning the clinician to withdraw the needle. If bloody pericardial fluid is removed, it should not clot and generally has a hematocrit lower than that of intravascular blood. Whenever possible, a thoracic surgeon should be notified that the pericardiocentesis is being performed in case a complication occurs requiring immediate surgical drainage.

Adding echocardiographic guidance to the pericardiocentesis has increased the success rate in obtaining fluid for diagnosis and relieving symptoms to almost 97% and has decreased the complication rate (95,118). Major complications include coronary artery laceration, myocardial puncture, pneumothorax, trauma to abdominal organs (especially the liver), and even death. The complication rate in collected series of pericardiocentesis using echocardiographic guidance is 2.4% with no deaths (118). The hazards of the procedure may be minimized if it is performed only on patients with a significant anterior clear space greater than 1 cm, using echocardiographic guidance, correcting thrombocytopenia prior to the procedure, and avoiding obviously loculated or posterior effusions (95,118,119).

Pericardiocentesis by itself is considered only an initial temporizing procedure to obtain diagnostic fluid and relieve symptoms. It is particularly useful in stabilizing a patient's condition before surgical drainage is performed. However, pericardiocentesis is not considered to be definitive treatment, since most (39–56%) malignant effusions will recur even after single or repeated taps (95,118). Insertion of a small no. 7 or no. 8 French multihole pigtail catheter over a guidewire into the pericardial space can be easily accomplished at the time of initial tap, to allow intermittent drainage over several days. Still, a large number of patients treated in this manner will require more definitive surgical drainage for long-term control of the effusion (95).

One word of caution is highlighted by two recent reports of large-volume pericardiocenteses on patients in tamponade. Wolfe and Edelman noted transient, severe, symptomatic systolic dysfunction in two women, lasting 1–2 weeks after they had undergone pericardiocentesis (650ml bloody pericardial fluid removed from either patient) to relieve a tamponade for a malignant pericardial effusion from metastatic breast cancer (126). Both patients were treated symptomatically and recovered gradually. Braverman and Sundaresan (127) reported a similar picture in a 27-year-old woman with a pericardial tamponade from benign acute pericarditis who was noted to have global myocardial dysfunction after undergoing pericardiocentesis that removed 500 ml serous fluid. A subxiphoid pericardial window was subsequently made, with removal of 1000 ml more fluid. Dobutamine was used to treat her low-output syndrome, which resolved completely 3 weeks later. The cause of this phenomenon, which we have also seen, is not known, but it may relate to diminished coronary blood flow during the period of tamponade, leading to a degree of myocardial stunning that was eventually reversible.

Intrapericardial Sclerosis

The logical extension of pericardiocentesis with catheter drainage is injection of a sclerosing agent into the pericardium through the indwelling catheter to prevent a recurrence of the effusion, much like that practiced with malignant pleural effusions. Almost half of the pleural sclerosis agents listed in Table 28-5 have been used in various small series intrapericardially. Agents were chosen on the basis of their irritating qualities and/or their antitumor activity, but the mechanism of action of the successful agents is unknown.

Nitrogen mustard, thiotepa, and quinacrine were tried in the 1970s in small studies with fair results but with pain and substantial toxicity from bone marrow suppression, leading to abandonment of these agents (41). Intrapericardial tetracycline, the most widely used drug, has had a combined success rate of 85% in the two largest reports (128,129). Tetracycline was instilled in doses of 500 mg–1 g on several days in all patients (mean, 2.9 days), and the pericardial catheters remained in place for a mean 8.8 days in one of the studies (128). Although a fairly effective agent with the expected toxicities of fever (18.7%), pain (9.9%), arrhythmias (12.1%), and catheter plugging (4.4%), tetracycline had the distinct disadvantage of requiring a long hospitalization. Tetracycline is no longer available, and the analog now used, doxycycline, has had a 100% success reported in one small series of seven patients, but they too required multiple instillations (130). The most recent series using pericardial sclerosis as primary management was larger, involving 85 patients, and had a 73% success rate in controlling the effusion for over 30 days (131). This group used tetracycline early in the series and doxycycline later, but as in prior reports, multiple instillations of drug were also necessary for success.

Bleomycin has also been used in very small series (a total of 15 patients in five series) with fairly good results and minimal toxicity, although these small patient series are difficult to interpret (118). Other anecdotal reports of cisplatin, teniposide, and fluorouracil have also appeared, although such small series preclude drawing any conclusions about efficacy and safety.

Immunostimulators interleukin-2 (132) and OK-432 (133) have also been employed by intrapericardial infusion to control malignant effusions. The results from these small series suggest that in twothirds of patients, the effusion can be controlled. However, this novel approach appears to offer no advantage over other agents (118).

One primary concern about the advisability of intrapericardial sclerosis is whether there is an increased risk of pericardial constriction in patients so treated. Lee and associates reported their favorable experience with intrapericardial sclerosis in 20 patients using mitomycin C, and had a 70% success rate (134). Soon afterward,

however, the same group reported that in one of their initially successful cases, the patient developed constrictive pericarditis 6 months later. They noted that this complication may occur if the patient survives long enough after pericardial sclerotherapy (135). Despite this concern, late pericardial constriction has not been commonly reported.

Intrapericardial radioisotopes, including gold and chromic phosphate, have been used (95,118). They are only partially effective even in radiosensitive tumors, and the logistical problems associated with them have precluded their use. In a novel approach, radioactive iodine (^{131}I) has been tagged to a monoclonal antibody (HMFG2) with intrapericardial administration, and the preliminary excellent results in a small series of four patients suggest that this technique bears further investigation (136).

Radiotherapy

External beam radiotherapy has been advocated for a variety of tumors with cardiac and pericardial involvement (137). In collected series (118), most patients underwent initial pericardiocentesis followed by radiotherapy in the 1500–4000 cGy dose range, the threshold at which radiation pericarditis and myocarditis can appear (98,138,139). Approximately 67% of patients so treated will have a positive response, although the best results are found with lymphomas and leukemias (118). Pericardial inflammation is a complication of therapy and may lead to acute pericarditis or possibly late constriction. Generally, radiotherapy is recommended for patients with radiosensitive tumors without hemodynamic compromise, who have not previously received radiotherapy (95).

Surgical Approaches

Since pericardial tamponade is predominantly a mechanical problem related to compression of the heart by an effusion, it is not surprising that the earliest attempts to treat this problem involved a surgical approach to drainage, and surgery has remained the preferred technique, although it has been considerably refined. In 1649, Jean Riolan first suggested trephination of the sternum to decompress a pericardial effusion compressing the heart, although the technique was not used until several centuries later (140). In 1819, Romero performed the first successful surgical pericardiotomy (141). However, it was Napoleon's famous surgeon, Baron Dominique-Jean Larrey, who first used the subxiphoid approach to drain the pericardial cavity, considering this an easy operation with small risk. He believed, as we do today, that this most dependent portion of the pericardium was best, since the collection of fluid was more prominent and the heart was at the greatest distance away from the pericardium, with the least chance of a rhythm disturbance (142). Techniques have advanced during the intervening 150 years, although Larrey's approach is still favored.

The term *window* in reference to pericardial surgery was described first by Williams and Soutter in 1954 in their description of an anterior thoracotomy through which they created a small opening in the pericardium and held it open by suturing it to the lung (143). The term *subxiphoid pericardial window* was finally used by Fontanelle and associates in 1970, and that term has continued to the present (144).

Subxiphoid Pericardiectomy (“Window”)

The most popular approach to surgical treatment of a malignant pericardial effusion is the subxiphoid pericardiectomy, which offers the distinct advantages of very low mortality (1% or less), 1% major morbidity, 100% immediate efficacy in relieving tamponade, and a long-term recurrence rate of 3–7% (41,95,119,145). Diagnostic accuracy is also excellent and approaches 100%, since fluid and pericardial tissue are both removed and are sent for pathological evaluation. In critically reviewing surgical series, it is important to consider only reports of surgery performed in the last 10 years or so, in the era of the most modern anesthetic techniques, so that the assessment of results reflects current practice with its lower risks. The most recent report involved 82 patients with malignant pericardial effusion who underwent subxiphoid pericardiectomy (146). No postoperative deaths were attributable to the surgical procedure, and there was only a 2.4% recurrence rate in the long term requiring further intervention.

Subxiphoid pericardiectomy may be performed in the operating room in only 30–45 minutes on critically ill patients under local anesthesia. Often general endotracheal anesthesia is used if there is no significant hemodynamic compromise or if the pericardium has been decompressed by pericardiocentesis. With general anesthesia, exposure is improved and a larger portion of pericardium may be removed because there is greater muscle relaxation (145). In addition, general anesthesia is necessary if there is extreme obesity or a narrow costal angle, or if there has been a previous upper midline incision. In fact, in these circumstances it may be preferable to divert to a left anterior thoracotomy for the pericardiectomy.

For the subxiphoid approach, a short 4- to 6-cm midline incision is made, extending caudad from the xiphoid with entrance into the preperitoneal space after the linea alba has been opened. After fluid has been collected for cytology, the pericardium is explored with the finger to find tumor nodules and to break up loculations. Recurrence of the effusion is best prevented when a large 4 cm × 4 cm portion of pericardium is removed for pathological examination (95). Pericardial tubes can be then inserted anterior and posterior to the heart before the wound is closed. The tubes are left in place 2–3 days until the drainage is 50–100 ml/day. Commonly, patients are discharged home on the second or third postoperative day.

Occasionally, no obvious tumor nodules are seen on the pericardium when it is visualized directly through the wound. In this situation, the diagnostic yield may be improved with pericardioscopy using a rigid or flexible scope, which can be used to better inspect the rest of the pericardium to obtain directed biopsy specimens of suspected lesions (147). Three of 40 patients in the series of Millaire and associates had suspected malignancies confirmed by pericardioscopy alone at the time of surgery, that would have otherwise been missed (147).

Although the term *pericardial window* implies that the communication remains open to drain the pericardium, it is not clear that this is actually the mechanism of action. A subxiphoid pericardiectomy (“window”) drains into the preperitoneal space, and probably it seals fairly soon. Sugimoto and associates (148) examined this question in following up their series of 26 patients who had undergone a subxiphoid pericardial window procedure. They found by echocardiography that there was thickening of the pericardium/epicardium and obliteration of the pericardial space. Autopsies of four patients who eventually died of their cancer a mean of 120 days after the procedure confirmed the fusion of the visceral and parietal pericardia. These workers concluded that the mechanism allowing success with this procedure is not the maintenance of a “window” draining the effusion continuously, but rather an inflammatory reaction causing fusion of the pericardium to the epicardium, obliterating the former space. They emphasized the necessity of keeping the pericardial space decompressed by suction postoperatively until the fluid drainage is minimal (<50 ml/24 hours) to keep the two pericardial surfaces in opposition to allow fusion.

Left Anterior Thoracotomy and Pericardiectomy

The left anterior thoracotomy for pericardiectomy is quick to perform, has a low morbidity and mortality, and allows examination and biopsy of the contents of the left pleural cavity if desired (125). The procedure is performed through a 10-cm long submammary incision entering the chest through the fifth intercostal space just lateral to the sternum. The pericardium is removed from just anterior to the left phrenic nerve over to the right mediastinal pleural reflection.

Some studies suggest that the amount of pericardium remaining after surgical drainage of the pericardium is directly related to the frequency of development of postoperative complications and recurrent effusion (102). Nevertheless, in collected series of pericardiectomy by left anterior thoracotomy (118), the overall success rate was 83% (freedom from recurrent effusion) and the mortality. was 13%—not as favorable as the results with subxiphoid pericardiectomy. The other primary disadvantage of the left anterior thoracotomy is that it is major thoracotomy requiring general anesthesia (118), and it also may be technically difficult to perform because of adhesions in the occasional patient with a lung cancer in the left pleural cavity who has been treated with radiotherapy.

Currently, the left anterior thoracotomy for pericardiectomy is preferred for benign effusive pericarditis, as occurs with purulent pericarditis and viral pericarditis. Benign pericarditis has a propensity to late constriction if most of the pericardium is not removed initially when surgery is performed. Conversely, a subxiphoid pericardial window is generally not recommended for drainage of benign and perhaps some malignant pericardial effusive disease when the patient is expected to have a significant life span (102,118,119).

Median Sternotomy with Pericardiectomy

The median sternotomy is an even more extensive procedure and gives very wide exposure to most of the pericardium. This approach is preferred only for constrictive pericardial disease, which may occur in the cancer patient as the late result of radiation pericarditis, extensive tumor mass or cake, or possibly as the result of a late failure from a previous approach to pericardial drainage (125). Because of the risk of myocardial laceration and significant bleeding, most surgeons prefer to have cardiopulmonary bypass on standby when dealing with constrictive pericarditis.

One of the most important technical points in the performance of a pericardiectomy for constriction is to remove the pericardium over the left side of the heart first to prevent the acute pulmonary edema that may occur if the right side of the heart is decompressed first, which would allow increased blood flow to the constricted left ventricle (125). In addition, it is important to continue the pericardial resection down to include the cavae to release them; otherwise, the right-sided failure symptoms may persist postoperatively.

Thoracoscopic Pericardiectomy

The recent advent of videothoracoscopic surgery has allowed the surgeon to perform many previously open procedures using this minimally invasive approach (149). Pericardiectomy for effusive disease has proved to be technically feasible with videothoracoscopy, with a recent series of 28 patients by Liu and associates demonstrating 100% long-term success, no significant morbidity, and 0% mortality (150).

Videothoracoscopy has the disadvantages of requiring the lateral decubitus position, minimally increased operating time, and a double-lumen endotracheal tube, and the surgeon must have substantial videothoracoscopic experience to perform this procedure effectively and safely. However, this approach is ideal in the patient with simultaneous pulmonary or pleural pathology that needs evaluation and treatment (such as with a pleural abrasion or talc poudrage), a recurrent or loculated pericardial effusion, previous heart surgery or subxiphoid pacemaker insertion, or a previous substernal esophagogastrostomy (150). The videothoracoscopic pericardiectomy may also be performed from either the right side or the left side of the chest. Technically, a large area of pericardium may be removed, as much as 6 cm × 8 cm, including pericardium posterior to the phrenic nerve if needed for complete drainage (125).

Pericardioperitoneal Shunt

An additional alternative drainage method was reported by Wang and associates (151) in a small series of four patients. They used the Denver pleuroperitoneal shunt to drain the pericardium into the peritoneal cavity. They performed the procedure with the patients under local anesthesia; the mean hospital stay was 2.8 days in these shunt patients. Further results in larger groups of patients will be needed before any conclusions can be made about the efficacy and safety of this technique.

Percutaneous Balloon Pericardiotomy

Palacios and associates in 1991 reported a novel approach to drainage of pericardial effusions using a percutaneous balloon pericardiotomy (152). The pericardium is entered by a conventional subxiphoid pericardiocentesis. A guidewire is advanced into the pericardium, over which a Mansfield 20mm × 3 cm dilating balloon is passed to a point where it straddles the pericardium and is then inflated to create a pericardial window. Usually the pericardial fluid drains into the pleural cavity, as indicated by a new pleural effusion. A catheter is then left in the pericardium until the drainage is minimal.

In their first 50 cases (153), successful, long-term decompression of the effusion was accomplished in 92%, with the rest requiring surgery on an urgent or emergent basis. A new left pleural effusion requiring treatment occurred in 16% of patients, and 4% required a chest tube for a pneumothorax. Another 11% developed a fever, but no pericardial infection was found. The current experience by this group includes 88 patients with a success rate of 88% (154). Experience with this new technique thus far is limited to just a few investigative groups. However, the results look promising, especially in patients with recurrent effusions, and this technique bears close observation over the next few years.

Recommendations

A malignant pericardial effusion is a not uncommon complication of advanced cancers, particularly with cancer of the lung and breast and lymphoma/leukemia. The effusion can rapidly progress to tamponade and if unrecognized may lead to death. Prompt decompression of the effusion has been shown to markedly improve the quality and quantity of life. However, the optimal method of accomplishing this objective is not easily determined because of the difficulty in comparing the large number of nonrandomized series with heterogeneous patient populations employing various techniques and having varying criteria for successful clinical response. No treatment modality clearly emerges as the preferred technique. In addition, therapy to some extent must be individualized, depending on the tumor cell type and its sensitivity to chemotherapy or radiotherapy, the performance status of the host and expected length of survival, and whether the patient presents with pericardial tamponade. Our recommendations are as follows:

1. In a patient without hemodynamic compromise and a chemosensitive tumor, such as lymphoma, leukemia, testicular cancer, or small cell lung carcinoma, systemic chemotherapy should be given. If symptoms or tamponade appear, then a pericardiocentesis should be performed, possibly followed by subxiphoid pericardiectomy. If chemotherapy fails and the tumor is also radiosensitive, then radiotherapy should be considered as the next step.

2. Patients with a symptomatic, suspected, or proven malignant pericardial effusion, a reasonable life expectancy (3 months or more), and no tamponade should be considered for an elective subxiphoid pericardiectomy. If tamponade and hemodynamic compromise are present, a decompressing pericardiocentesis should be performed and a subxiphoid pericardiectomy should be performed the next day. If the institutional resources are such that surgical decompression is unavailable, a suitable approach would be intrapericardial sclerosis with bleomycin or doxycycline, although a higher failure rate should be expected.

3. Very poor candidates for surgery, on the basis of comorbid disease, such as severe chronic obstructive pulmonary disease, should be considered primarily for intrapericardial sclerosis. Patients with a very short life expectancy (less than 1 month) should also be considered for intrapericardial sclerosis.

4. In patients with a history of malignancy and who develop a pericardial effusion in which the diagnosis is uncertain, or when pericardial tissue is necessary for a histologic diagnosis, an operative intervention by the subxiphoid, videothoracoscopic, or left anterior thoracotomy approach is indicated.

5. Videothoracoscopic pericardiectomy is indicated in the setting of coexisting pleural disease requiring evaluation and treatment or when a subxiphoid pericardiectomy is technically not advisable.

6. Patients in whom chemotherapy, radiotherapy, or intrapericardial sclerosis has failed should be managed by surgical pericardiectomy.

In general, patients with pericardial involvement by their primary cancer have an incurable disease. Nevertheless, most patients with symptomatic effusions should be offered treatment, because they usually will respond rapidly and often quite remarkably to pericardial decompression and will have a meaningful period of palliation outside of the hospital at home.

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29

CARDIOPULMONARY TOXICITY OF CANCER THERAPY

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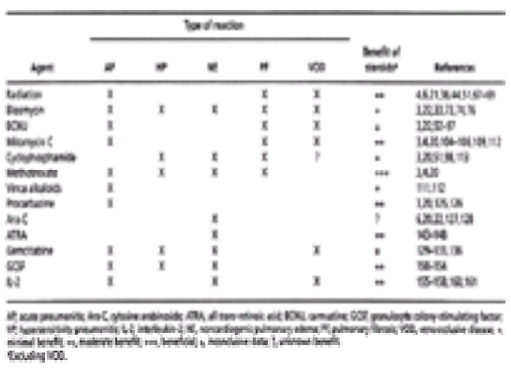
Advances in cancer therapy have produced increasingly complex combinations of chemotherapeutic agents, radiation therapy, and biological-response modifiers. New methods of providing hematopoietic support with growth factors and marrow products have minimized myelosuppression as a barrier to the dose intensification of chemotherapy. As a result, many patients are now at increased risk for cardiopulmonary toxicity. Some of these side effects develop rapidly after exposure to the inciting agent, whereas others take years before becoming evident. Consequently, the need for vigilant supportive care has intensified. Fortunately, progress also has been made in prevention and management of treatment-related toxicity. Optimal management depends on the early recognition of treatment-related toxicity so that the inciting agent can be withdrawn and the appropriate therapy instituted. In addition, patients who are successfully treated for a malignant disease need to be informed that they remain at risk for potentially late cardiopulmonary toxicity and strongly counseled to avoid smoking and other toxic exposures. With appropriate supportive measures, cardiopulmonary risks to patients who are undergoing intensive cancer therapy can be minimized despite the narrow therapeutic index of this treatment.

PULMONARY TOXICITY

Severe pulmonary injury can result from radiation therapy or chemotherapy alone or in combination (Table 29-1). The incidence of treatment-related pulmonary toxicity is variable and difficult to establish precisely (1). A small number of agents predictably cause toxicity, whereas most do so exceedingly rarely. Because chemotherapy is usually given in multi-drug combinations and is often given concurrently with radiation, there may be additive or synergistic toxicity (2). The severity of toxic reactions varies widely, ranging from incidental asymptomatic cases to life-threatening respiratory insufficiency. The predominant patterns are interstitial pneumonitis with pulmonary fibrosis, acute hypersensitivity reactions, and noncardiogenic pulmonary edema. Other, less common acute pulmonary syndromes are pleuritis and bronchospastic anaphylactic reactions (3,4,5 and 6). Interstitial infiltrates may also be the presenting feature of a wide variety of other complications of malignancy, infectious as well as noninfectious (Table 29-2).



Agent	Type of reaction: AP	HP	NE	PF	VOD	Benefit of steroids*	Reference
Radiation	X			X	X	**	4,6,71,78,44,51,97–99
Bleomycin	X	X	X	X	X	+	2,72,73,74,76
BCNU	X			X	X	+	2,72,727–97
Mitomycin C	X			X	X	**	3,4,97,104–104,109,112
Cyclophosphamide		X	X	X	?	+	2,29,91,98,113
Methotrexate	X	X	X	X		***	3,4,20
Vinca alkaloids	X					+	111,112
Procarbazine	X					**	3,29,105,126
Ara-C				X		?	4,20,22,127,128
ATRA				X		**	142–148
Gemcitabine	X	X	X		X	+	129–133,136
GCSF	X	X	X			**	158–154
IL-2	X		X		X	**	155–158,160,161

AP, acute pneumonitis; Ara-C, cytosine arabinoside; ATRA, all trans-retinoic acid; BCNU, carmustine; GCSF, granulocyte colony-stimulating factor; HP, hypersensitivity pneumonitis; IL-2, interleukin-2; NE, noncardiogenic pulmonary edema; PF, pulmonary fibrosis; VOD, venoocclusive disease; +, minimal benefit; ++, moderate benefit; +++, beneficial; ?, inconclusive data; ?, unknown benefit.
*Excluding VOD.

TABLE 29-1. PULMONARY TOXICITY OF COMMONLY USED CYTOTOXIC AGENTS AND ROLE OF CORTICOSTEROIDS

Infection
Drug reaction
Radiation toxicity
Lymphangitic tumor spread
Leukemic infiltration
Pulmonary edema
Adult respiratory distress syndrome
Pulmonary emboli
Leukoagglutinin reaction
Diffuse alveolar hemorrhage
Idiopathic pneumonia syndrome

TABLE 29-2. DIFFERENTIAL DIAGNOSIS OF DIFFUSE INTERSTITIAL INFILTRATES IN CANCER AND BONE MARROW TRANSPLANT PATIENTS

APPROACH TO THE PATIENT WITH PNEUMONITIS

Typically, a subacute onset of progressive dyspnea, nonproductive cough, anorexia, and low-grade fever develops 1–3 months after treatment with chemotherapy and radiation (6). High fever (>40°C), purulent sputum, and hemoptysis are rarely seen and suggest an infectious etiology (7,8 and 9). Physical findings include tachypnea, tachycardia, diffuse rales, and occasionally cyanosis. Hypoxemia with respiratory alkalosis may ensue.

Chest radiographs usually reveal diffuse interstitial or alveolar infiltrates, particularly prominent at the lung base (3). However, infection is the most common specific diagnosis that is confirmed when diffuse infiltrates are manifested (10,11 and 12). Pulmonary function tests may display a restrictive pattern and decreased diffusing capacity (3). Decisions regarding the need for more invasive diagnostic procedures should be individualized. Patients who are neutropenic and those who have received prolonged corticosteroid therapy have a high risk of infection with bacteria and *Pneumocystis carinii*, respectively, and may be candidates for empirical therapy. Treated leukemia patients and bone marrow transplant (BMT) patients, on the other hand, may benefit from a more accurate diagnosis (13,14). Consideration of whether drug or radiation-related toxicity is present is made by assessment of the timing, risk factors, and agents involved and usually requires further confirmation by biopsy. Bronchoscopy is the preferred method for biopsy, as it is the least invasive. However, open-lung biopsy is sometimes necessary.

For infectious agents and malignant lesions, bronchoalveolar lavage (BAL) has a high diagnostic yield, although false-positive results have been seen with fungi and cytomegalovirus (15,16). Protected nonbronchoscopic BAL can be used effectively for intubated patients, and for severely immunosuppressed individuals it poses less risk of bleeding compared with transbronchial biopsy (12,17,18). Nonetheless, transbronchial forceps biopsy yields more tissue for histopathologic evaluation, which may increase the diagnostic yield in noninfectious processes.

If a diagnosis cannot be established by bronchoscopy, a thoracoscopic or open-lung biopsy may be required. Because a thoracoscopic procedure requires that

collapse of the lung be evaluated, it may not be feasible in some critically ill patients with limited pulmonary reserve. A trial comparing the relative usefulness of thoracoscopic and open-lung biopsies in noncritically ill patients found that equivalent amounts of tissue could be obtained with either method, producing similar diagnostic accuracy. Less morbidity occurred with thoracoscopy, however, and therefore this is the preferred procedure in patients who can tolerate single lung ventilation (19).

The histopathology of treatment-related interstitial pneumonitis incorporates nonspecific features that are common to drug- and to radiation-induced lung injuries. Capillary damage is present, characterized by endothelial swelling with fibrinous alveolar exudate in the interstitial and alveolar spaces. Type I pneumocytes are destroyed, and thus type II pneumocytes proliferate, sometimes with atypia. Characteristically, a paucity of mononuclear inflammatory cell infiltration is present. Release of inflammatory cytokines such as transforming growth factor-b recruits and activates fibroblasts. This culminates in thickening of alveolar septa by collagen and the development of fibrosis (3,6,20,21). In addition, hypersensitivity reactions may show eosinophilic infiltrates or granuloma formation (3,20,21 and 22). Leakage of plasma proteins into the alveolar space contributes to a loss of compliance and abnormal gas exchange.

Most patients in whom clinically evident pulmonary disease develops present several months after completion of treatment. Aggressive therapies have improved survival for many patients, leading to an increase in observed late toxicities. Evaluation of delayed toxicities has been extensively reviewed in patients with childhood acute leukemia and Hodgkin's disease (23,24,25,26,27,28,29 and 30). Risk factors for delayed toxicity were dose-intensified therapy and spinal irradiation (24,25). Asymptomatic restrictive lung disease may be evident by pulmonary function testing at the completion of therapy and may persist for greater than 10 years (23,24 and 25,27).

DELAYED-ONSET PNEUMOPATHIES

Syndromes that have a delayed onset include pulmonary fibrosis, pulmonary veno-occlusive disease (VOD), and bronchiolitis obliterans with organizing pneumonia. Pulmonary fibrosis usually develops as a progressive disorder in patients who have had acute pneumonitis. The fibrotic process generally plateaus after several months, but if a sufficiently large amount of lung is affected, it may lead to the development of cor pulmonale.

VOD is a rare disorder that is characterized by endothelial damage and intimal fibrosis of pulmonary veins and venules, resulting in pulmonary hypertension. Clinical presentation includes progressive dyspnea, hypoxia, and signs and symptoms of cor pulmonale. Pulmonary VOD typically occurs 2–4 months after therapy (31). However, isolated cases of early-onset pulmonary VOD have been reported (32). Diagnosis typically requires open-lung biopsy with special stains for elastic tissue. Although several etiologic factors have been associated with this syndrome, a handful of cases have been attributed to radiation and chemotherapeutic agents, including bleomycin, BCNU (carmustine), mitomycin C, and possibly cyclophosphamide (8,33).

Bronchiolitis obliterans is a circumferential inflammation of the terminal air spaces that can be caused by a diverse array of causes, including infections, toxins, medications, and autoimmune and other inflammatory conditions. A limited number of reports have been published of bronchiolitis obliterans complicating chemotherapy or radiation. Patients usually present several months after completion of therapy with fever and cough in addition to dyspnea. Most cases of bronchiolitis obliterans that are associated with radiation have occurred in patients who were treated for breast cancer (34,35). Radiographic findings may be minimal or may include acinar or reticular infiltrates. In contrast to the typical pneumonitis that is associated with radiation, the infiltrates extend outside the radiation port.

Patients must be educated about the risks of delayed effects of aggressive treatment regimens. It is essential to encourage continued screening for late effects and avoidance of detrimental health behaviors (smoking, respiratory exposures). Early detection and intervention can lead to minimization of delayed effects of therapy.

SPECIFIC CAUSATIVE AGENTS

Radiation Therapy

Irradiating the lung parenchyma results in acute as well as chronic lung injury, consisting of acute respiratory toxicity, interstitial pneumonitis, and later pulmonary fibrosis (4,21,36). Deaths due to pneumonitis have been reported (37). Overall, the incidence of symptomatic pneumonitis ranges from 5% to 10% of patients treated with mediastinal irradiation (6,38,39 and 40). The risk varies widely depending on the treatment plan, however, and approaches 20% in patients who are treated for lung cancer, whereas it is only 1% in individuals irradiated for breast cancer (41,42). Interstitial pneumonitis can occur within hours of treatment but typically is observed 2–3 months after completion of radiotherapy (43).

The risk of injury is dose and volume related. In nearly all patients, subtle changes on x-ray and pulmonary function can be detected (41). For clinically significant toxicity, however, there appears to be a threshold effect, with symptoms unlikely unless the volume of lung irradiated exceeds 10% or >200 cm^2. In addition to the volume of lung treated, the total dose of radiation and the number of fractions are important factors. Risk increases if daily dose fractions of radiation exceed 2 Gy or if the total dose to the lung is greater than 60 Gy using conventional fractionation and two-dimensional treatment planning (4,43,44).

Approaches that have been developed to enhance the effectiveness of radiation include the delivery of multiple doses of radiation daily, three-dimensional treatment planning, and administration of radiation concurrently with chemotherapy. Delivery of smaller doses of radiation two or three times a day is defined as a *hyperfractionated schedule*. Although the use of smaller fractions should decrease the risk of fibrosis, hyperfractionated schedules also deliver a higher weekly dose rate of radiation and frequently a higher total dose. These factors can negate any benefit from the use of smaller fractions (45).

Three-dimensional conformal radiotherapy uses computed tomography (CT) to contour treatment volumes and delivers the radiation beams from multiple portals. Multiple CT images are used to delineate the target and the normal structures, and the dose is delivered by several cross-firing beams that intersect at the target center from multiple angles. This approach reduces the amount of radiation that is delivered to normal lung surrounding the tumor and allows for the delivery of higher doses without increasing complication rates (39,46).

Several studies suggest that the delivery of chemotherapy concurrently with radiation is more effective than treatment with chemotherapy followed by radiation for patients with lung cancer (47). Concurrent delivery of chemotherapy with radiation can potentiate the risk of pulmonary toxicity (6,48,49 and 50). Chemotherapeutic agents that are particularly likely to increase the risk of pulmonary toxicity of radiation include dactinomycin, bleomycin, cyclophosphamide, cisplatin, vincristine, and recombinant interferon-a. For cisplatin, small daily doses or continuous infusion schedules appear to be safer than larger intermittent bolus dosing, suggesting that the risk may be related to peak plasma concentration (51).

Additional factors that are associated with increased risk of pulmonary toxicity following radiation are withdrawal of steroids and prior radiation to the lung (47). Continued tobacco use during treatment has actually been associated with a decreased risk in some studies (52,53).

A number of approaches to predict which patients will develop symptomatic pulmonary toxicity following radiation have been developed. Mathematical models that estimate the dose and distribution of exposure to normal lung based on the CT images (dose volume histograms), with or without inclusion of perfusion imaging to correct for the functionality of this lung volume, are useful for evaluating competing three-dimensional conformal treatment plans. Some models have been helpful in predicting increased risk of pneumonitis (39,54,55 and 56). The baseline pulmonary function, especially the diffusing capacity of carbon dioxide, has been shown to predict risk of postradiation impairment, and algorithms that incorporate baseline physiological function and the magnitude of normal lung irradiated are being developed (55,56 and 57). Serum markers that reflect the extent of parenchymal damage or the inflammatory response to radiation are also being evaluated. Baseline or posttreatment changes in the serum concentration of surfactant, tumor growth factor-b, and thrombomodulin have been shown in small studies to predict patients in whom pulmonary toxicity will develop and may play a role in determining which patients can be safely given higher doses of radiation (58,59,60,61,62 and 63).

The clinical features of radiation pneumonitis are nonproductive cough, dyspnea, fever, pleuritic or substernal chest pain, malaise, and weight loss. On examination few physical findings are usually found, although some patients have rales or a pleural rub. Purulent sputum or a leukocytosis is uncommon and is helpful in differentiating radiation injury from pneumonia. Frank hemoptysis is rare at presentation but has been observed as a late complication of radiation (64,65). The diagnosis is suggested by chest radiography demonstrating abnormalities within the radiation port. Typically, a diffuse haze is identified within the treatment area that progresses to patchy alveolar infiltrates and air bronchograms (66,67) (Fig. 29-1). CT, especially with a high-resolution protocol, is more sensitive than plain radiography in identifying subtle changes early in the course of the disease (4). Gallium scanning may also demonstrate abnormalities before the chest radiograph does. The magnitude of decline in pulmonary function tests often corresponds with the clinical symptoms and consists of reduced lung volumes and compliance and abnormalities in gas exchange (68).

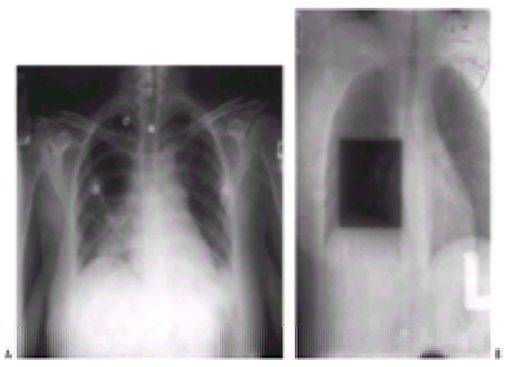


FIGURE 29-1. Radiation pneumonitis. Unilateral alveolar infiltrate in a woman following radiation treatment for recurrent Hodgkin's disease (A). This opacity corresponds with the radiation port (B).

Treatment with corticosteroids can reduce the acute inflammatory response of pneumonitis. Prednisone is administered at 60 mg/day for 2 weeks and then gradually tapered. This produces improved symptoms and resolution of pulmonary infiltrates in most patients (6,68,69). The sudden withdrawal of corticosteroids, as is done in some chemotherapy protocols, may precipitate acute pneumonitis in patients who are receiving radiation. This should be avoided by tapering the corticosteroids after each cycle (47). Amifostine reduced the incidence of acute pneumonitis in one small randomized study from 23% to 4% in patients aggressively treated for lung cancer with hyperfractionated radiation and concurrent chemotherapy (70). In animal models, angiotensin-converting enzyme inhibitors, pentoxifylline, a-tocopherol, and antibodies against CD40 ligand have been shown to ameliorate radiation pneumonitis but have not yet established a role in the clinic (71,72).

Although acute pneumonitis sometimes resolves completely, with or without treatment, in most patients some degree of pulmonary fibrosis subsequently develops (47,67). Fibrosis is generally detected between 6 months and 2 years after radiotherapy. Symptoms are usually minimal, unless the patient had significant pretreatment lung disease or involvement of more than 50% of one lung (6). Symptoms include dyspnea, cyanosis, clubbing, and cor pulmonale. Chest radiographs reveal a dense infiltrate with volume loss; a characteristic feature is a straight border to the infiltrate delineating the radiation port. Corticosteroid therapy is rarely helpful in this chronic phase (47).

Chemotherapy

Bleomycin

Although it is one of the few cytotoxic agents that is not myelosuppressive, serious toxicity from bleomycin occurs in the form of dose-related pulmonary fibrosis, as well as hypersensitivity reactions that are unrelated to dose (3,22). At therapeutic doses, the incidence of bleomycin-related pulmonary fibrosis ranges from 3% to 5%, but rates as high as 40% have been reported for some intensive regimens (3,20,22,73,74). The cumulative dose is the strongest predictor of toxicity, and above 350–500 units, the incidence of pulmonary abnormalities rises sharply, to above 10% (3,6,20,73,74). Other risk factors for the development of toxicity include age older than 70 years; prior lung disease; radiation concurrent with, preceding, or subsequent to bleomycin administration; tobacco use; impaired renal function; and the use of high inspired concentrations of oxygen (3,22,75,76,77 and 78). Hematopoietic support with granulocyte colony-stimulating factor during treatment with bleomycin-containing chemotherapy has been associated with an increased risk of pulmonary toxicity in some, but not all, series (79,80,81 and 82).

Clinical findings include progressive dyspnea, dry nonproductive cough, tachypnea, basilar rales, and a pleural friction rub. Fever and peripheral blood eosinophilia may be present in acute hypersensitivity reactions (3,74). Chest radiograph findings range from fine infiltrates to nodular infiltrates and lobar consolidation (Fig. 29-2). Before the onset of symptoms or radiographic changes, a decrease in diffusing capacity and forced vital capacity can be detected. The presence of a polymorphonuclear alveolitis on BAL is supportive, but a biopsy is necessary to confirm the diagnosis.

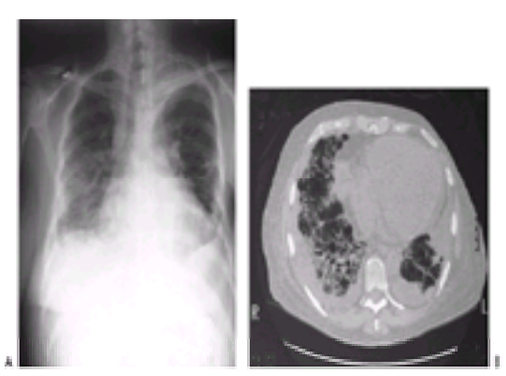


FIGURE 29-2. Bleomycin lung.The chest radiograph shows bilateral reticulonodular infiltrates and pleural thickening (A). Computed tomographic findings include bibasilar air cysts, bronchiectasis, and reticular opacities associated with extensive bilateral pleural thickening (B).

Patients who are treated with bleomycin should have baseline pulmonary function tests before therapy. They should receive a test dose 12–24 hours preceding the first treatment dose to minimize the risk of a hypersensitivity reaction. Total lifetime dosing should not exceed 400 units. Pulmonary function tests should be repeated if an elevated creatinine develops (77). Bleomycin should be discontinued if pulmonary function declines by 15%. Most patients with early or mild abnormalities stabilize or improve with discontinuation of the drug, but those with severe toxicity (resting hypoxemia and extensive infiltrates on x-ray) have a high mortality. Corticosteroids are probably beneficial for patients with bleomycin-induced pulmonary toxicity, particularly for hypersensitivity reactions (3,20,22,83). Aggressive diuresis may be necessary in cases of acute pulmonary edema (84). Amifostine, urokinase-type plasminogen activator, angiotensin-converting enzyme inhibitors, niacin, and soluble tumor growth factor-b receptor have been shown to be useful in animal models but have not been tested in the clinic (85,86,87 and 88).

Patients who have been treated with bleomycin-based regimes should be monitored closely throughout their lifetime during any surgical procedures, as oxygen therapy can exacerbate bleomycin toxicity. Adult respiratory distress syndrome (ARDS) has been reported in patients following general anesthesia and occurs 3–10 days after surgery (89,90). The preoperative forced vital capacity is the best predictor of postoperative complications. Perioperative prophylactic steroids, concentration of intravenous fluids into the least volume possible, and use of the lowest possible oxygen concentrations during mechanical ventilation are measures that can reduce the risk of complications (84,89).

BCNU

The pulmonary toxicity of BCNU (carmustine) has been unambiguously documented, because it is used as a singleagent treatment of malignant brain tumors, which are a group of diseases that spare the lungs and often present in otherwise healthy patients. At conventional doses, the incidence of toxicity ranges from 20% to 30%, with a clear dose–response effect (3,20,91,92). Pulmonary toxicity develops in up to 50% of patients at cumulative doses that exceed 1500 mg/m^2 (20). Typical BCNU pulmonary toxicity has an insidious onset, similar to that of other subacute chemotherapy drug reactions. The median onset of presentation is within 90 days of treatment (91,92,93 and 94), but some patients are diagnosed as late as 10–20 years after the completion of chemotherapy (95). Radiographic abnormalities occur late, if at all. BAL may reveal interstitial pneumonitis, but a lung biopsy is required for definitive diagnosis (93,94).

High-dose BCNU is commonly used in conditioning regimens for BMT. At single doses greater than 450 mg/m^2, there is a precipitous increase in the risk of acute interstitial pneumonitis (96,97). When used in preparative regimes that include other alkylating drugs, BCNU doses of 600 mg/m^2 result in symptomatic pulmonary toxicity in more than half of the patients treated (68,93,98).

Patients should be periodically monitored with pulmonary function tests and the drug withdrawn if a decline in function is noted. For patients who are already taking steroids for their underlying malignancy, discontinuation of BCNU is the mainstay of treatment for pneumonitis (3,20,99,100). Mortality in this setting is approximately

16% (101). In contrast, the pulmonary toxicity due to BCNU-based dose-intensive regimens responds well to steroids and has a better prognosis (94,102). Patients are generally treated with prednisone at doses of 1 mg/kg for 10 days and then slowly tapered to avoid a reexacerbation of symptoms (94,103). Complete recovery can be expected in the majority of these patients.

Mitomycin C

The incidence of severe mitomycin C pulmonary toxicity ranges from 3% to 29% (8,20,104,105 and 106). Patients usually present with the insidious onset of dyspnea and a dry cough 3–6 months after completion of therapy. In some cases, bronchospasm, pulmonary edema, or hemorrhage ensues (4,107,108). Diffuse pulmonary infiltrates are evident radiographically. Pulmonary function tests reveal decreased diffusing capacity and restrictive ventilatory defects. Toxicity is related to cumulative dose and usually develops after four cycles of therapy when the total dose exceeds 20–30 mg/m^2 (109,110). Underlying lung disease, tobacco use, oxygen therapy, and chest irradiation increase the risk of pulmonary side effects (3,8). Synergistic toxicity is observed when mitomycin is used in combination with vinca alkaloids (111,112). Although most patients respond initially to steroid therapy, many go on to develop chronic pulmonary dysfunction (110,112). Increasing the steroid dosage is effective in some cases (104,110). Patients who are able to taper off of steroids within 1 month have a decreased risk of developing chronic dysfunction. Those who require a more protracted tapering schedule are more likely to have progressive toxicity (110). Mortality approaches 50% (3,20). In addition to causing direct lung injury, mitomycin is associated with a hemolytic-uremic syndrome, which is rarely complicated by pulmonary hemorrhage (108).

Cyclophosphamide and Other Alkylating Agents

Cyclophosphamide is one of the most frequently prescribed chemotherapeutic drugs, and at standard doses the associated incidence of symptomatic pulmonary toxicity is <1% (3). However, if sought, physiological changes in lung function can be demonstrated in many patients. For example, in a study of 150 patients with breast cancer who received the combination of cyclophosphamide, doxorubicin, and 5-fluorouracil (5-FU), the mean diffusing capacity of the lungs for carbon monoxide was decreased by 12% after three cycles (98). The risk of toxicity increases when higher than standard doses are used or when cyclophosphamide is administered with other DNA–damaging drugs or radiation. Treatment of small cell lung cancer with high doses of cyclophosphamide followed by radiation led to symptomatic pulmonary fibrosis in 74% of patients (113). Currently, pulmonary toxicity is most commonly seen in the setting of BMT (98). Clinical features are similar to those of other drugs, although fever is often prominent (3). Radiography typically shows a basilar reticular pattern; occasionally, a pattern of diffuse pulmonary edema is observed. BAL demonstrates a cellular inflammatory response (98). Corticosteroids may hasten improvement in some cases, and the overall recovery rate is approximately 60% (3,20,47). A closely related agent, ifosfamide, has rarely been associated with interstitial pneumonitis (114).

Although the therapeutic applications of other alkylating agents, such as chlorambucil, busulfan, and melphalan, are not as broad, each has been reported to cause pulmonary toxicity. All have been associated with the insidious onset of dyspnea and reticular infiltrates months to years after therapy. Unlike cyclophosphamide, chlorambucil and busulfan toxicity appear to be dose related (3,6). The role of corticosteroids for pulmonary toxicity from these agents is equivocal, although a trial of therapy in symptomatic patients is indicated (3,20).

Vinca Alkaloids

During or shortly after the infusion of vinca alkaloids, bronchospasm can occur. The chest radiograph may show evidence of interstitial infiltrates. Treatment consists of bronchodilators, steroids, and other supportive measures. The incidence of this reaction has been reported to be as high as 5% for vinorelbine and is less common with other vinca alkaloids (115,116). The risk of pulmonary toxicity is increased when vinca alkaloids are given with mitomycin (111,112,117,118 and 119). For example, Rivera et al. (112) reported an incidence of 4% for severe acute respiratory distress within 4 hours of receiving a dose of vinca alkaloid in 378 patients treated for advanced non–small cell lung cancer. Mitomycin C was administered on the same day in only one-third of the cases. Most patients had wheezing, rales, rhonchi, and new diffuse interstitial infiltrates on chest radiography. Significant improvement occurred within 24 hours in 21 of 25 patients who were managed with supplemental oxygen and bronchodilators. Eight patients who received corticosteroids for persistent dyspnea all improved; however, residual chronic dyspnea was worse than before treatment in 63% of patients, and one patient died (112). Rechallenge with vinca alkaloids has resulted in recurrence of symptoms (111,112).

Doxorubicin

When administered alone, doxorubicin is not associated with pulmonary injury. It may, however, reduce the tolerance of the lung to radiation. Enhanced toxicity has been identified in patients with Hodgkin's disease, breast cancer, and small cell lung carcinoma treated with doxorubicincontaining regimens and with irradiation (8,120,121). When doxorubicin is administered after chest irradiation, severe pneumonitis can occur, even outside the radiation port (122). This phenomenon, termed *radiation recall*, was described in a report of 71 patients who received combined radiation therapy and chemotherapy with cyclophosphamide, doxorubicin, and vincristine. Pneumonitis was the primary toxicity, with a 15% incidence of ARDS and a mortality of 10% (122). A 7% incidence and 4% mortality from ARDS were reported when a doxorubicin-containing combination was resumed after a course of radiation (123). Corticosteroids have been reported to be effective treatment for radiation recall pneumonitis (122).

Methotrexate

Methotrexate has been associated with hypersensitivity reactions, pulmonary fibrosis, noncardiogenic pulmonary edema, and pleuritis. These reactions may develop after oral, intravenous, or intrathecal administration, and synergism with other toxins may occur (3,124). The presentation of methotrexate pulmonary toxicity may be fulminant, with fever, blood eosinophilia, rash, and rapid onset of respiratory failure (Fig. 29-3). The onset may be as early as 12 days and as late as 18 years after treatment (4). Pulmonary eosinophilia may occur, and histopathology often reveals a marked inflammatory infiltrate with granulomas. Nonetheless, the prognosis is favorable. Dramatic responses to corticosteroids have been reported (3,20).

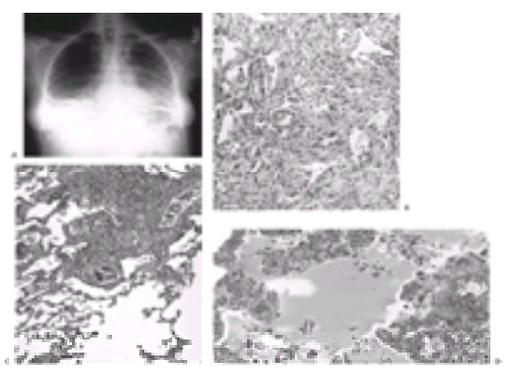


FIGURE 29-3. Methotrexate pulmonary toxicity. Alveolar infiltrates, primarily in the bases and bilateral pleural effusions, characterize this disease (A).These radiographic findings are consistent with either acute pneumonitis, hypersensitivity pneumonitis, or noncardiogenic pulmonary edema. These entities can be distinguished only by the clinicopathological findings (B–D). Acute pneumonitis produces expansion of the alveolar walls by a polymorphous inflammatory cell infiltrate. In this section, the pneumocytes exhibit moderate atypia (B). With hypersensitivity pneumonitis, there may be patchy interstitial lymphocytic infiltrates and associated bronchiolitis and granuloma formation (C). The pathological findings of pulmonary edema include expansion of the alveolar spaces by proteinaceous fluid (D).

Procarbazine

A hypersensitivity reaction characterized by the abrupt onset of respiratory distress along with fever, rash, arthralgias, and peripheral blood eosinophilia has been described in association with procarbazine therapy (3,20). The subacute onset of dyspnea over 1–2 weeks, without other signs of hypersensitivity, has also been reported (125,126). Corticosteroids appear to be beneficial in most cases (3,20,125,126).

Cytosine Arabinoside

Noncardiogenic pulmonary edema and ARDS have been associated with cytosine arabinoside (6,20,22,127,128). Pleural and pericardial effusions are present in a minority of cases. A dose–response effect appears to occur, with a 20–30% incidence after cumulative doses above 24 g/m^2. Management consists primarily of aggressive supportive care. The role of corticosteroids is unclear (22).

Gemcitabine

Pulmonary toxicity that is associated with gemcitabine is usually mild and self-limiting. However, it may produce life-threatening toxicity presenting as pneumonitis (129), acute hypersensitivity reaction with bronchospasm (130), ARDS (131,132), or capillary leak syndrome (133). Clinically evident toxicity occurs in 4–10% of patients (134,135). Symptoms usually develop within the first 24 hours after administration, but delayed reactions of up to 1 week have been reported (136,137). An increased risk of gemcitabine toxicity occurs when it is administered in regimens with docetaxel (138), concurrently with radiation therapy as a radiation sensitizer (135,139,140), or in patients with a prior history of reactive airway disease or previous radiation therapy to the mediastinum (135). Symptoms include dyspnea, cough, hypoxemia, and fever. Diffuse infiltrates on chest radiography are consistent with pulmonary edema. Transbronchial biopsies may reveal interstitial pneumonitis (132). Symptoms usually resolve with discontinuation of treatment. Corticosteroids, bronchodilators, and diuretics are effective in some patients (129,132,133,141,142).

Retinoic Acid Syndrome

All *trans*-retinoic acid (ATRA) syndrome is a life-threatening toxicity that occurs in up to 25% of patients with acute promyelocytic leukemia treated with ATRA. It resembles a capillary leak syndrome. It is characterized by fever, respiratory distress, and interstitial pulmonary infiltrates, often accompanied by weight gain, peripheral edema, pleural and pericardial effusions, and hypotension (143,144). Chest radiography shows bilateral interstitial and alveolar infiltrates (Fig. 29-4). Onset has varied from 2 to 35 days after the start of therapy. Although most affected patients have an elevated white blood cell count to ³20,000/µl, a significant percentage do not have a leukocytosis. In a review of 413 patients who were newly diagnosed with promyelocytic leukemia, ATRA syndrome developed in 64, 13 required mechanical ventilation, and four deaths were reported (145). Once respiratory distress is established, leukapheresis, chemotherapy, or cessation of ATRA provides no benefit. The early institution of high-dose steroids (dexamethasone, 10 mg intravenously every 12 hours for at least 3 days) results in prompt recovery in most patients (146,147 and 148), although respiratory failure can occur (149).

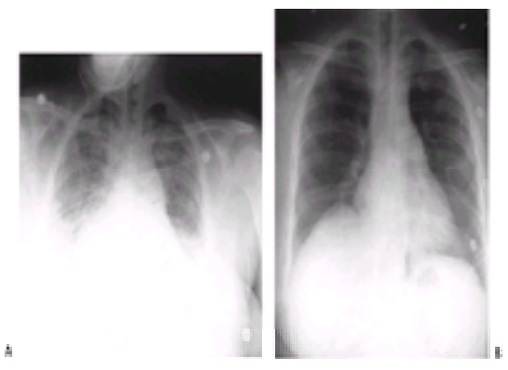


FIGURE 29-4. Retinoic acid syndrome. Rapid onset of bilateral pleural effusions and diffuse parenchymal infiltrates (A) that resolved with supportive measures (B).

Biological Response Modifiers

The availability of hematopoietic growth factors during the past decade has allowed the doses of chemotherapy to be further intensified. Sporadic reports of interstitial pneumonia (150,151), ARDS, and acute respiratory insufficiency (152,153) have appeared, generally in patients who also received chemotherapy that may have contributed to toxicity (80,151,154). Symptoms develop approximately 10 days after chemotherapy administration and coincide with recovery of the leukocyte count (150,151). The risk of toxicity increases above the age of 60 and does not appear to be dose related, although it is correlated with an elevated neutrophil count (124,150,151). Symptoms include abrupt onset of dyspnea and fever (150,152). Treatment with corticosteroids usually yields a prompt recovery. However, Couderc and associates (152) report that, despite high-dose corticosteroid therapy, two patients experienced progressive dysfunction and died of pulmonary fibrosis.

High-dose interleukin-2 (IL-2) is reported to cause severe respiratory distress with diffuse interstitial infiltrates (155). Pulmonary toxicity may also present as capillary leak syndrome leading to pulmonary edema (156,157,158 and 159). The risk of toxicity is dose dependent, occurs most frequently after the first intensive dose of therapy, and declines with subsequent dosing (160). Presenting symptoms include acute-onset shortness of breath, dyspnea, fever, eosinophilia, hypoxia, and pulmonary congestion. Onset is within 40 hours of dose administration (160). Treatment is supportive, with oxygen, diuretics, and steroids that usually produce a complete response (161).

Miscellaneous

Sporadic reports of life-threatening pulmonary toxicities have appeared for fludarabine (162,163), mitoxantrone (164), nilutamide (165,166), irinotecan (CPT-11)(167,168), and antithymocytic globulin (169). Oral etoposide has been associated with interstitial infiltrates and respiratory failure. Onset may occur within 14 days of treatment and has been effectively treated with steroids (168,170,171). The taxanes (paclitaxel and docetaxel), or the cremophor vehicle, have been associated with anaphylactoid reactions characterized by hypotension, dyspnea, bronchospasm, and urticaria (5,138,172). Reactions may develop during or within hours of completion of the infusion. Premedication with corticosteroids, antihistamines, and H2-antagonists have markedly reduced the incidence of this reaction (4,173).

Pulmonary Complications of Bone Marrow Transplantation

Pulmonary complications affect 40–60% of BMT recipients and are responsible for more than 30% of transplant-related deaths (174,175). In addition to the multiple infectious and noninfectious pulmonary side effects discussed already, there are further complications that are unique to these patients.

In the early phase of bone marrow recovery, diffuse alveolar hemorrhage may occur in up to 20% of patients and is associated with a mortality of as high as 80%. Symptoms and signs include progressive dyspnea, hypoxia, and diffuse patchy infiltrates, but rarely hemoptysis. The diagnosis is confirmed when BAL yields recovery of progressively bloodier aliquots that demonstrate hemosiderin-laden macrophages (175). Diffuse alveolar hemorrhage is associated with white blood cell recovery with or without thrombocytopenia. Risk factors include advanced age, underlying solid tumors, irradiation, severe mucositis, and renal insufficiency. Prompt diagnosis and institution of high-dose corticosteroids may be beneficial (175,176).

Interstitial pneumonitis is the most common pulmonary complication of marrow transplantation, occurring in 40% of allogeneic, 17% of syngeneic, and 10% of autologous transplant recipients (31). Cytomegalovirus accounts for most infectious cases. In 30–50% of patients, no infectious cause is identified. This noninfectious pneumonitis, termed *idiopathic pneumonia syndrome*, generally occurs after engraftment and is thought to be related to immunological reactions coupled with toxicity from conditioning regimens. Corticosteroids have no proven benefit, and the mortality remains close to 80% (31,68,175,177). A less severe interstitial pneumonitis has been observed with some of the preparative regimens that are used for autotransplant. This pneumonitis may respond to corticosteroids and is rarely fatal (68).

Acute graft-versus-host disease (GVHD) principally affects the skin, liver, gastrointestinal tract, and immune system; however, respiratory tract involvement may occur as well. Lymphocytic bronchitis is a controversial entity described in up to 25% of patients with acute GVHD (174). Whether it is a specific manifestation of GVHD, however, remains unresolved. Lymphocytic bronchitis presents with dyspnea and nonproductive cough, with a normal chest radiograph and without evidence of airflow obstruction. Bronchoscopy reveals diffuse inflammation of the airways. Pathological evaluation demonstrates small lymphocytes infiltrating the proximal bronchial mucosa, with loss of cilia and damage to the submucosal glands and goblet cells, predisposing to bacterial tracheobronchitis and pneumonia. Increased immunosuppressive therapy for the associated acute GVHD generally improves the syndrome (174,178).

The leukoagglutinin or pulmonary transfusion reaction is noncardiogenic pulmonary edema caused by activation of the recipient's neutrophils by donor leukocyte antibodies. The clinical presentation is respiratory distress, tachycardia, fever, chills, and often cyanosis and hypotension developing during administration of blood products. After discontinuation of the transfusion, treatment is supportive, and in most cases recovery is complete within a few days (179).

Bronchiolitis obliterans has been described in 10–20% of BMT patients, associated with chronic GVHD in most cases (31,174,178). This complication usually occurs 4–12 months after BMT and is manifested by exertional dyspnea, nonproductive cough, and wheezing. Because of airflow obstruction with gas trapping, physical examination may demonstrate late inspiratory rales, and pulmonary function tests may show obstruction in addition to restriction. BAL demonstrates lymphocytosis and excludes infection. Pathology resembles that of lung allograft rejection. Although mortality is as high as 65%, treatment with increased immunosuppressive therapy

appears to be beneficial if administered early in the course of disease (31,178,180).

Interstitial pulmonary fibrosis occurs in 20–30% of patients within 12 months of allogeneic BMT (174,178). Factors that contribute to diffuse lung injury and lead to fibrosis may include conditioning regimens (e.g., BCNU, busulfan, cyclophosphamide, and total body irradiation), immunosuppressive therapy (methotrexate), transfusion reactions, pulmonary hemorrhage, and hyperleukocytosis. Treatment is supportive, and the mortality remains high (174). In severe cases, successful lung transplant has been performed (27,181).

CARDIAC TOXICITY

Mediastinal irradiation and many chemotherapy drugs can produce cardiotoxicity (Table 29-3). Advances in radiation techniques along with the development of cardioprotective agents have reduced the risk of heart damage from some of these therapies. As new treatment modalities are introduced, however, predicted or unanticipated cardiotoxicities may be observed. As a result, vigilance for and management of cardiac side effects will remain an important component of supportive care for the foreseeable future.

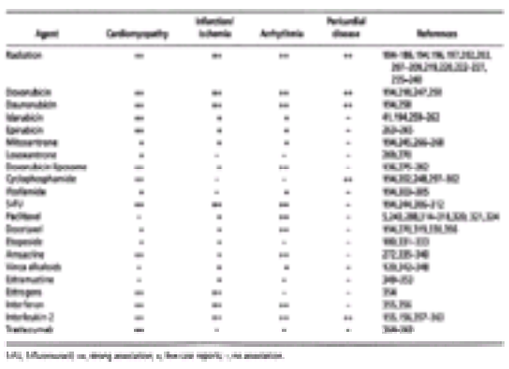


TABLE 29-3. CARDIOTOXICITY OF CANCER THERAPEUTIC AGENTS

Radiation Therapy

Mediastinal radiation therapy is an integral part of the treatment for Hodgkin's disease and other lymphomas and lung and breast cancer. The risk of damage to the heart from radiation therapy is related to the volume of the heart that is irradiated and the total dose received (182,183,184,185,186 and 187). Radiation therapy potentially can damage the pericardium, myocardium, coronary arteries, and conduction system. However, the incidence of all these toxicities is declining, with current dose fractionation and cardiac-shielding techniques that limit exposure (188,189).The use of anteroposterior and posteroanterior ports for Hodgkin's disease has minimized cardiac exposure (190). Minimizing exposure of the internal mammary node chain in patients with breast cancer has also limited cardiac exposure (191). The cardiotoxic effects of irradiation may be manifested early after completion of therapy, as with acute pericarditis, or delayed for years, as with coronary artery disease. Table 29-3 discusses the cardiotoxicity of cancer therapeutic agents.

Pericardial Disease

The diagnosis of toxicity can be made by chest radiography, CT scan, magnetic resonance imaging, echocardiography, angiography, electrocardiography (ECG), or biopsy. On chest film, the transverse diameter of the heart may be decreased, with narrowed or straight borders indicating fibrosis (192), or the cardiomediastinal ratio may be decreased, indicating cardiomyopathy or pericardial effusion (193). However, a normal chest radiograph does not exclude injury, as the majority of patients have no changes. Echocardiography, CT, and magnetic resonance imaging are more sensitive to evaluate the pericardium (192).

Although pericardial disease is the most common cardiotoxicity of mediastinal radiation, this complication occurs less often with modern treatment techniques (184,185,194,195,196,197 and 198). Pericardial disease, previously identified in up to 20% of patients when the entire pericardium was irradiated, was reduced to 7.5% with partial cardiac shielding and 2.5% with the addition of subcarinal blocking (199). During the course of treatment of a radiosensitive mediastinal mass, an acute pericarditis may occur, which is believed to be directly related to tumor response rather than pericardial damage. The patient usually presents with acute chest pain, fever, and ECG changes. Symptoms resolve despite continued treatment, and there is no correlation with the development of chronic pericarditis (190,196).

Typically, the onset of symptomatic pericarditis, pericardial effusion, or constriction is delayed for 4–9 months, but it may develop as late as decades after treatment (186,190,200,201 and 202). Symptoms include fever, pleuritic chest pain, and pericardial friction rub. The risk of developing a delayed pericardial effusion ranges from 2% to 10% at doses >4000 cGy (192,203). Factors that contribute to the development of the effusion are an elevated lymphocyte count >1500/µl, the presence of a large mediastinal mass, and concomitant chemotherapy (204). Most cases of radiation pericarditis resolve spontaneously within 16–20 months (185,194,205). Nonsteroidal antiinflammatory drugs can be used to provide symptomatic relief (185,186). Steroids may help in resolution of symptoms, but withdrawal may trigger relapse or identification of other inflammatory cardiac processes (201,206). The development of a pericardial effusion increases the risk of chronic pericardial disease. Of patients who become symptomatic, tamponade develops in 10–30%, usually within 2 years of treatment. Up to 20% progress to constrictive pericarditis within 5–10 years, although a 45-year latency period has been described (185).

In a few patients, the pericarditis is effusive and constrictive. This entity presents with signs and symptoms of pericardial tamponade. Right atrial pressure is persistently elevated after pericardiocentesis due to fibrosis of the visceral pericardium. Pericardectomy is required in most symptomatic patients with effusive-constrictive pericarditis (195). Despite aggressive surgical intervention, deaths have been reported due to persistent constriction and restrictive cardiomyopathy (207).

Myocardial and Valvular Disease

Myocardial damage, when detected, is usually mild and asymptomatic (185,198,208). The mechanism of injury is thought to be due to injury of the capillary endothelial cell, leading to obstruction of capillary blood flow, microvascular insufficiency, and myocardial fibrosis (186). Impaired exercise capacity with reduced resting ejection fraction may be identified on echocardiogram after completion of mediastinal radiation (193,202,209,210). Most patients have return of function within 2–6 months of completion of therapy (193,211,212). However, subtle changes have been reported several years after completion of treatment for Hodgkin's disease (213). Clinically evident heart failure is rare with the use of modern techniques (186,187). The concurrent or sequential use of anthracyclines may cause additive or synergistic toxicity to the myocardium (185,188,214,215). When radiation is delivered with doxorubicin, toxicity occurs at a dose that is 1000 cGy lower than when radiation is delivered as a single modality (216). Doxorubicin is also known to persist in myocardial tissue for months and may produce a “recall phenomenon” when radiation is delivered (217). Reduction of the anthracycline dose when used in combination therapy is recommended (218). If heart failure develops, treatment includes the use of inotropes and afterload reducing agents (187).

Valvular damage, although rare, may occur as a result of valvular thickening (185,186,196,197,219,220). The aortic valve followed by the mitral valve is most frequently involved, and stenosis and regurgitation can occur (207,219,220). In an analysis of 635 patients who were treated for Hodgkin's disease, 29 patients developed murmurs in follow-up (196,197). Women who receive radiation for breast cancer are at higher risk of developing valve disease when they are irradiated for left-sided lesions (221). Although most patients are asymptomatic (196,197,221), deaths due to valve failure have been reported (196,197). The onset of detection is between 11 and 16 years after completion of the radiation (219). Diagnosis is best made by echocardiogram (219). Valve replacement is sometimes necessary; however, the procedure may be complicated by fibrosis of surrounding tissue (219).

Coronary Artery Disease

Long-term follow-up studies indicate that patients who have received mediastinal irradiation characterized by accelerated atherosclerosis and vessel fibrosis have an increased risk of developing coronary artery disease (184,189,194,196,197,207,222,223). The vessels that are most commonly involved are the right coronary, left main, or left anterior descending coronary artery (189). The incidence of ischemic heart disease ranges from 2% to 12% (196,198,203,224,225,226 and 227). The risk, which is related to dose and volume of the heart exposed (203,225), has been reduced with modern techniques and smaller doses of radiation delivered to the coronary arteries (224). Occlusive coronary lesions are usually identified 6–12 years after therapy (224,227,228). Coronary artery disease may present in patients with no other cardiac risk factors (207). Coronary spasm may also occur (229). In an autopsy series that involved patients younger than the age of 35, 25% of irradiated

individuals versus 2.5% of age- and sex-matched nonirradiated control subjects had significant coronary artery disease (230). Large studies demonstrated a 2.6- to 8.8-fold relative risk of mortality from myocardial infarction after mediastinal radiation for Hodgkin's disease (194,198,203,224,225,231). The increase in mortality is not apparent until 10 years after irradiation. Patients at the highest risk of death from myocardial infarction are those who receive radiation at an age less than 20 years (196,197). Rutqvist et al. (232) found a threefold relative risk of death from ischemic heart disease in women with cancer of the left breast who received a highdose volume of radiation before mastectomy compared with surgical control subjects. No increased risk was found for those who received radiation to the right breast or those treated with electrons postoperatively and received lower doses to the myocardium (232). Monitoring and early intervention for signs of coronary artery disease are warranted for patients who have received irradiation to the chest. Every attempt should be made to reduce other risk factors for arthrosclerosis in patients who have received mediastinal radiation. Coronary artery bypass surgery and balloon angioplasty have been successful in patients with radiationinduced coronary artery disease (228,233). The growth factor fibroblast growth factor-b, administered during mediastinal radiation, decreased blood vessel stenosis and increased survival in an animal model but has not yet been tested in the clinic (234).

Conduction System Disease

Atrioventricular blocks are the most commonly reported conduction disorders following mediastinal radiation (202,235). Conduction disturbances, ECG changes (ST-T segment changes, decreased QRS voltage), and arrhythmias have been reported (185,190,236,237,238 and 239). In an estimated 20–30% of patients who are treated with mediastinal radiation, conduction disorders develop within 10 years of treatment (185,240). ECG changes are evident in 10–15% of patients with Hodgkin's disease who are treated through a single port (196,197). This is decreased to 2.5% when more conventional divided ports are used (241). In some patients with breast cancer who are treated for a left breast lesion, evidence of heart block develops (221). The risk increases at doses greater than 40 cGy and in those patients with preexisting coronary risk factors. Patients with pacemakers are at particular risk for development of arrhythmias due to damage to the device and interference in conduction signals (194,242).

Chemotherapy

Doxorubicin

Doxorubicin generates free radicals intracellularly that can cause myocardial membrane damage. The damage is complicated by chemotherapy-induced reductions of glutathione, which serves as a free oxygen scavenger (243). Doxorubicin exposure and cardiotoxicity have a welldocumented dose–response relationship. Von Hoff et al. (218) reviewed 4018 patients who were treated with doxorubicin and identified an exponential increase in cardiac toxicity with increasing cumulative doses. The probability of developing congestive heart failure (CHF) increased from 3% at 400 mg/m^2 to 18% at 700 mg/m^2 (218). Other studies have confirmed this dose–response effect (244,245). However, there is some degree of interpatient variability. CHF has been reported after total doses of only 40 mg/m^2, whereas other patients have received more than 1000 mg/m^2 without complication (218). Risk factors that have contributed to toxicity are a bolus schedule of administration (246), previous or concurrent mediastinal irradiation (247), very young or advanced age, a history of cardiac disease, female sex, and concomitant cyclophosphamide administration (218,244,248). Doxorubicin that is administered to children younger than age 4 is associated with thinning of the left ventricular wall as a result of inhibition of myocardial growth (249).

Toxicity may develop as acute, subacute, or late cardiotoxicity. Acute toxicity occurs within hours or days of dose. Patients may present with ECG changes, arrhythmias, pericardial effusion, CHF, and pericarditis with myocardial dysfunction (247,250) (Fig. 29-5). ECG changes have been identified in 20–30% of patients who receive doxorubicin. Rarely, sudden death following administration has been reported (251). Patients with symptomatic atrial or ventricular arrhythmias should not receive antiarrhythmic therapy (248).

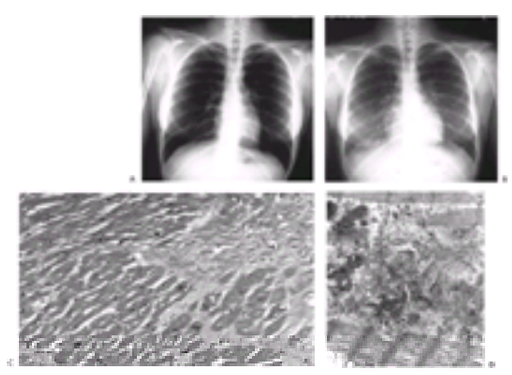


FIGURE 29-5. Doxorubicin cardiomyopathy. Films taken 3 weeks apart show the development of cardiomegaly and the ground glass infiltrates of pulmonary edema secondary to doxorubicin cardiomyopathy (A, B). Biopsy (C) depicts myocytes with enlarged and atypical nuclei associated with interstitial fibrosis. Electron microscopy (D) shows myofibril fragmentation, mitochondrial degeneration, and the accumulation of whorls of membrane proteins (×15,300) (C).

The peak time for the onset of subacute toxicity is 3 months after the last dose of therapy (218,252). Patients may present with evidence of CHF, such as tachycardia, fatigue, dyspnea, or pulmonary edema. A careful evaluation can reveal underlying abnormalities even in asymptomatic patients. Of asymptomatic patients who receive 500–600 mg/m^2 doxorubicin, subacute toxicity develops in 2–20% (218,244,250). Mortality ranges from 30% to 60% (253,254 and 255). With aggressive medical management, cardiac dysfunction usually slowly improves (245,256).

Late toxicity presents 5 or more years after the chemotherapy (194,256,257). It may be due to decompensation of a previously identified toxicity or it may develop in patients who have been without previous symptoms (194,256,257). Patients may present with arrhythmias, fibrosis, and hypertrophy. Late toxicity correlates with increased cumulative doses of doxorubicin and mediastinal irradiation (194,247). Reports of death have occurred up to 15 years after treatment (256,257).

Other Anthracyclines and Related Drugs

The cardiotoxicity that is caused by other anthracyclines has clinical and pathological features similar to those observed with doxorubicin. The clinical spectrum ranges from asymptomatic decreased myocardial contractility to heart failure or myocardial infarction. The threshold at which the risk of toxicity significantly increases is approximately 600 mg/m^2 for daunorubicin (258), 150 mg/m^2 for idarubicin (41,259,260,261 and 262), and 900 mg/m^2 for epirubicin (263,264). Epirubicin toxicity may occur as early as 8 weeks after treatment; however, a decline of left ventricular ejection fraction (LVEF) is uncommon earlier than 4 years (265) and often returns to normal limits after completion of treatment (263).

Mitoxantrone is an anthracenedione with antitumor activity similar to that of doxorubicin. Although mitoxantrone has been touted to be less cardiotoxic than doxorubicin, the nonhematological dose-limiting toxicity is also cardiotoxicity (266,267). This cardiotoxicity is cumulative, with a rapid increase in risk observed above a total dose of 160 mg/m^2 . Prior anthracycline exposure of >250 mg/m^2 increases the risk of toxicity (245,268).

Losoxantrone, an anthrapyrazole, is similar in structure to the anthracyclines and was developed due to its lower potential for causing cardiotoxicity. No relationship appears to exist between the total cumulative dose of losoxantrone and change in LVEF. In one study of patients with breast cancer, CHF developed in 1%, and 4% experienced a >20% asymptomatic decline in LVEF (269). In a dose escalation study of losoxantrone in combination with paclitaxel, CHR developed in one patient, and a >10% reduction in asymptomatic LVEF developed in nine additional patients (270).

Strategies to Reduce the Risk of Anthracycline Cardiotoxicity

The primary mechanism of treatment is prevention. Baseline imaging of myocardial contractility should be obtained for all patients. Monitoring by echocardiogram or MUGA should begin as the cumulative dose approaches the threshold dose or earlier if other risk factors for cardiovascular disease are present (194,249,271). Patients with an LVEF of <30% should not be treated with an anthracycline. Furthermore, if the LVEF is reduced 10–15% during the course of treatment, anthracycline chemotherapy should be discontinued (194,271).

The risk of cardiotoxicity caused by anthracyclines is related in part to peak plasma concentrations of the drug. Continuous infusion schedules produce lower peak plasma levels than bolus infusion and as a result are less cardiotoxic (218,244,272,273). Shapira and associates (274) demonstrated a decline in LVEF of 6% when 6-hour infusions were used to administer a total cumulative dose of 400 mg/m^2. However, a 21% reduction in LVEF was identified when therapy was administered by

20-minute bolus infusion (274). It is unclear whether different administration schedules produce differences in efficacy (194). Other strategies that ameliorate anthracycline cardiotoxicity include encapsulation within liposomes and the concurrent administration of cardioprotectants such as dexrazoxane.

Compared with the bolus administration of free drug, liposomal encapsulation results in an improved pharmacokinetic profile with a longer plasma life and better drug delivery (275,276). Liposomal doxorubicin is taken up preferentially by the reticuloendothelial cells and tumors and is less likely to be deposited in cardiac muscle (277,278 and 279). The liposomal encapsulation permits the administration of high doses of doxorubicin, without increased cardiotoxicity (136,280). Following a median dose of liposomal doxorubicin of 500 mg/m^2 (range, 192–900 mg/m^2), only 1 of 41 patients had evidence of CHF, and in this patient a biopsy was consistent with a nonanthracycline etiology (280). Liposomal doxorubicin, however, may produce acute allergic reactions (275,276,281,282).

Dexrazoxane is approved for use with anthracyclines and mitoxantrone (169,283,284,285,286,287,288 and 289). It is rapidly taken up by myocytes and converted intracellularly into a chelating agent that binds to free and bound iron, reducing anthracycline-iron complexes that contribute to the generation of toxic oxygenfree radicals (290,291,292 and 293). In previously untreated patients, differences in cardiac function can be detected by radioisotope scans after a cumulative dose of doxorubicin of 150 mg/m^2 . Inclusion of dexrazoxane into regimens that contain anthracyclines may reduce the cardiotoxicity by as much as 50%, with the effect becoming apparent after a cumulative dose of 300 mg/m^2 (294). Cumulative doses of doxorubicin that exceed 1000 mg/m^2 along with dexrazoxane have been given to patients without resultant cardiac damage (283).

Although dexrazoxane allows the dose intensity of anthracyclines to be increased, in most studies this has not led to improvement in overall survival (290,292,295,296). Rather, patients experience increased noncardiac toxicities, particularly myelosuppression, secondary to the increased dose intensity (284). Whether dexrazoxane impairs the antitumor activity of the anthracyclines remains unsettled. Several randomized trials that involved patients who were treated with doxorubicin found no difference in response rates (287,296). However, two randomized trials of patients with breast cancer found a decrease in the response rate when dexrazoxane was administered to individuals who had received cumulative doxorubicin doses of <300 mg/m^2 (291,294). As a result, dexrazoxane currently is indicated only for patients who have received a total dose of doxorubicin of >300 mg/m^2 for whom continued therapy is warranted. The recommended dose of dexrazoxane is 10:1 with doxorubicin and 30–60:1 with mitoxantrone. Dexrazoxane should be infused over 15 minutes, beginning 30 minutes before the anthracycline (287,288,294,296).

Cyclophosphamide

The dose–response relationship between cyclophosphamide and cardiac damage is noncumulative. As a single agent, cyclophosphamide is associated with cardiac complications almost exclusively at the doses used for BMT (120–270 mg/kg, in divided doses, over a few days). Cyclophosphamide toxicity may begin with transient ECG changes that include low voltage, depressed ST segments, elevated cardiac enzymes, and a reduced LVEF (297). More advanced toxicity consists of a myopericarditis that is characterized by coronary artery vasculitis, heart failure, hemorrhagic pericarditis, and effusion (298,299 and 300). Myocardial biopsy reveals capillary endothelial damage, myocardial hemorrhage, and necrosis with edema and serosanguineous pericardial effusion (202,299). The onset is fulminant, within 1 week of beginning treatment; the mortality is 20–40% (202,248,301).

Factors that influence the development of cardiotoxicity include dose, rate of drug delivery, previous exposure or concurrent administration of anthracyclines, underlying cardiac dysfunction, and mediastinal radiation therapy (194,297,298,302). Gottdiener et al. (202) evaluated 32 patients with hematological malignancies who were treated with 180 mg/kg cyclophosphamide over 4 days as part of a conditioning regimen for allogeneic BMT. Cardiotoxicity was common, with a 28% incidence of CHF, 19% incidence of pericardial tamponade, and 19% mortality. Furthermore, for patients who had received prior anthracycline therapy, the incidence of CHF was 50%. Goldberg et al. (301) reported on a series of 80 children who underwent allogeneic BMT for aplastic anemia or immunodeficiency syndromes, none of whom had prior anthracycline therapy or mediastinal irradiation. CHF developed in 25% of the patients who received more than 1.55 g/m^2 /day cyclophosphamide for 4 days, compared with 3% of patients who received <1.55 g/m^2 /day; nearly half of the cases were fatal.

With aggressive supportive care with diuretics, inotropic agents, and afterload reduction, patients who recover have no long-term sequelae (194,248). A baseline MUGA scan and continuous cardiac monitoring are indicated for patients who receive high-dose cyclophosphamide. Amifostine may offer protection against the cardiotoxicity that is associated with high-dose cyclophosphamide (85).

Ifosfamide

Although ifosfamide is an alkylating agent that is structurally related to cyclophosphamide, it produces a different pattern of cardiotoxicity. Supraventricular arrhythmias have been reported at doses of 6.25–10.0 g/m^2 over 3–5 days (303). In one patient, rechallenge with the drug resulted in a refractory arrhythmia (304). Ifosfamide is frequently used as part of the conditioning regimen for stem cell transplantation, and at these higher doses, more cardiac side effects are observed. In a retrospective study of 52 patients who were undergoing autologous transplant, cardiotoxicity developed in 17%. Although most patients had received prior treatment with doxorubicin, none had a history of CHF, angina, or arrhythmias before the chemotherapy. Symptoms occurred at 10–12 days. An elevated serum creatinine preceded the onset of CHF, suggesting that a delayed elimination of the drug may have contributed to the observed toxicity. Most patients required intensive care; one patient developed cardiogenic shock and died (305). Patients who receive ifosfamide should have kidney function tests frequently monitored to assure proper drug excretion.

5-Fluorouracil

Angina is the most common symptomatic reaction, occurring in 64% of patients who experience cardiac toxicity due to 5-FU (306). Arrhythmias, CHF, infarction, cardiogenic shock, and sudden death have been reported (307,308). Although the overall incidence of cardiotoxicity is low, it appears to be significantly higher in patients with underlying coronary artery disease (approximately 5% vs. 1% in patients without such a history). This is probably due to increased coronary vasomotor tone and spasm (244,309,310). Life-threatening ischemia has occurred among patients with normal coronary arteries (194,311). Mediastinal radiotherapy and continuous infusion schedules of 5-FU are risk factors for ischemia (309). The addition of leucovorin to 5-FU also increases the risk (312).

Most patients have reported typical precordial pain, sometimes radiating to the arms or jaw, which can be associated with nausea, vomiting, and diaphoresis. Abnormalities on ECG may include diffuse ST-segment depression or elevation, peaked T waves or T-wave inversions, prolongation of the QT interval, and atrial or ventricular arrhythmias. Toxicity can be progressive with repeated dosing (307,309). Clinical toxicities are usually identified after the third cycle of bolus infusion and during the first 3–4 days of a continuous infusion schedule (309). Symptoms generally start within hours of exposure to the drug and resolve after discontinuation of the 5-FU, spontaneously or after the administration of nitrates. Aggressive supportive measures with intravenous inotropic agents, diuretics, and vasodilators may be necessary. Although the ECG returns to normal in most patients, continued administration of 5-FU can lead to infarction. Reversible regional or global left ventricular wall motion abnormalities have been demonstrated. Although symptoms may improve with drug cessation, cardiomegaly is not always reversed (313). Neither nitrates nor calcium channel blockers have reliably demonstrated efficacy in preventing 5-FU–related ischemia (307,309). Relapses on reinstitution of therapy are frequent, and thus the risks and benefits of further treatment with 5-FU should be weighed carefully (194,311).

Paclitaxel

Initial reports of cardiotoxicity due to paclitaxel administration have been attributed to severe hypersensitivity reactions that occur within the first few minutes of infusion (314). Hypotension developed in as many as 25% of these patients and was linked to the cremaphor vehicle (5,315). The prophylactic use of steroids and histamine blockers has significantly reduced the severity of these reactions (316,317). Cardiotoxicity may also present as CHF, hypotension, arrhythmias, conduction disturbances, and ischemia (316,318,319 and 320). The most common finding is asymptomatic sinus bradycardia (318,320). This complication requires no treatment and does not preclude further use of the drug. Whether preexisting cardiac dysfunction is a predictor of toxicity remains controversial. Nevertheless, the risk for patients without cardiac risk factors is minimal. In a retrospective review of 3400 patients who were treated with paclitaxel as a single agent, the incidence of advanced heart block, atrial or ventricular arrhythmias, and myocardial infarction or ischemia was below 1% for all (318). The risk of toxicity does not appear to be related to cumulative dose (318). Patients in whom symptomatic arrhythmias or heart block have developed have been rechallenged safely under controlled conditions, which may include the use of continuous cardiac monitoring and pacemaker placement (318,320).

In contrast, if paclitaxel is given in combination with doxorubicin, the observed toxicity is dramatically increased, with ventricular dysfunction developing at significantly lower cumulative doses of doxorubicin (243). One way that paclitaxel potentiates the cardiotoxicity of doxorubicin is by decreasing doxorubicin clearance (288,321,322). Paclitaxel also increases cellular retention of doxorubicin (243,323). After just four cycles of chemotherapy (200 mg/m^2 paclitaxel each cycle and doxorubicin cumulative dose of 240 mg/m^2), 20% of patients experience a decline in LVEF below normal, and 4% have symptoms of heart failure. After eight cycles of therapy (doxorubicin cumulative dose of 480 mg/m^2), approximately 50% of patients have depressed contractility, and 20% experience symptomatic CHF (288). Results are similar for chemotherapy-naive individuals and for patients who are heavily pretreated with anthracyclines (324,325).

Different strategies have been used to decrease the pharmacokinetic interaction between paclitaxel and doxorubicin. Alteration in dose administration and substitution of epirubicin or losoxantrone for doxorubicin and docetaxel for paclitaxel have been recommended (270,319,326). The incidence of toxicity is reduced to <5% when the total cumulative dose of doxorubicin is kept below 360 mg/m^2 (321,323,325). Controversy remains over whether the duration of the paclitaxel infusion influences the risk of cardiac toxicity. Some reports indicate that pharmacokinetic interaction is decreased when paclitaxel is administered as a 3-hour infusion (243,327). If a

minimum of 4 hours elapses between administration of the agents, the toxicity is reduced (328,329). Because paclitaxel does not alter the pharmacokinetics of epirubicin, this is a less toxic combination than the paclitaxel-doxorubicin regimen (139,326). Another alternative is to use docetaxel rather than paclitaxel, since docetaxel does not alter the pharmacokinetics of doxorubicin (319,330).

Etoposide

A few reports of myocardial infarction and CHF during etoposide infusions have been published. Some patients had preexisting coronary artery disease, and others received doxorubicin, cisplatin, bleomycin, or mediastinal irradiation (180,331,332). Hypotension occurs frequently when etoposide is administered by an intravenous infusion that lasts less than 30 minutes but is reversible with intravenous fluids and lengthening of the infusion rate (333).

Amsacrine

Amsacrine (AMSA) is an agent that is used primarily in the treatment of acute nonlymphocytic leukemia. Toxicity results from the production of free radicals in a fashion similar to that of anthracyclines (334). Toxicity ranges from subtle ECG changes to arrhythmias, CHF, and myocardial infarction (272,335). The incidence of arrhythmias is below 1% but can result in sudden death (272,336,337). In one case, biopsy revealed infarction and myocardial necrosis in a patient who did not have underlying cardiac disease (338).

The risk of toxicity has been related to the total dose of AMSA, prior anthracycline exposure, and the rate of AMSA infusion (194). No evidence of cumulative dose effect has been found (336). In one series, when the combination of anthracycline and AMSA dose exceeded 900 mg/m^2 , abnormalities in cardiac function developed in most patients (339). Hypokalemia may be a risk for the development of arrhythmias (272,335). However, in a large review, most affected patients had normal serum potassium levels (336). In one study, AMSA was administered to patients with a prior history of arrhythmias, all of whom tolerated the infusion without incident if the potassium level was above 4.0 mEq/l (334,340).

Symptoms, usually presenting with the first course of treatment (336), may begin as the drug is being infused or within 4 hours (272,335). Echocardiographic changes and evidence of CHF appear within a week (339,341) and return to baseline on discontinuation of the drug (336,339,341). Symptoms of CHF may require the use of digitalis and diuretics (339).

Vinca Alkaloids

Several cases of myocardial ischemia or infarction have been reported in association with the combinations of vinca drugs with cisplatin and bleomycin (120,342,343). In some cases, cisplatin was believed to be the causative agent (120). In other reports, vincristine alone was associated with myocardial infarction (344,345). In addition to myocardial ischemia, vinca alkaloids have been associated with cardiac autonomic neuropathies that result in orthostatic hypotension and an abnormal heart rate response (346,347). These abnormalities were found more often among patients who received high cumulative doses (347) or inadvertent overdose (348).

Estrogens and Estramustine

Diethylstilbestrol, at doses of ³3 mg/day, is associated with CHF, myocardial ischemia and infarction, and thromboembolic episodes in up to 10% of patients (349,350 and 351). Lower doses (1 mg/day) retain activity against prostate cancer and are not associated with an excess incidence of cardiovascular events (350). Although the antineoplastic properties of estramustine are related to the inhibition of microtubule assembly, the cardiovascular toxicities appear to be linked to the estrogenic properties. The incidence of myocardial ischemia or infarction and cardiomyopathy is in the range of 10–30%, with the greatest risk reported in patients with prior cardiac disease (351,352 and 353). Cardiac complications are most evident during the first year of therapy and have been correlated with elevated luteinizing hormone levels (354).

Biological Response Modifiers

Interferons (a and g) and interleukins (IL-2) can produce cardiotoxicity (155,355,356,357,358 and 359). Interferon has been associated with supraventricular and ventricular arrhythmias, myocardial infarction, cardiomyopathy, and sudden death. Neither the dose nor the duration of therapy has been correlated with toxicity (355). The risk appears to be increased among patients with a prior history of coronary artery disease and in individuals who were previously treated with an anthracycline (360). Although most patients who experience atrial arrhythmias or myocardial ischemia have underlying heart disease, those in whom ventricular arrhythmias or cardiomyopathy develop may have had no such history. Onset of symptoms usually occurs within 5 weeks of treatment (355). Most toxicities resolve after discontinuation of the drug if the patient has no prior history of coronary artery disease (355), but irreversible cardiomyopathy has been reported in a patient who was previously treated with doxorubicin (356).

High doses of IL-2 cause a myriad of adverse events. The most serious event is the immediate onset of decreased systemic vascular resistance and capillary leak syndrome. This is characterized by hypotension, tachycardia, decreased LVEF, pulmonary and peripheral edema, oliguria, and renal failure (156,159). Cardiac toxicities have also included atrial and ventricular tachyarrhythmias, bradycardia, complete heart block, myocardial ischemia and infarction, myopericarditis, and, rarely, sudden death (155,156,357,359,361,362). Symptoms develop within 120 hours after the initiation of treatment and can last for up to several hours (363). Changes on ECG range from nonspecific ST-segment elevation (359) to arrhythmias in up to 10% of patients (155,156). No correlation has been found with prior cardiac dysfunction. However, a relationship appears to exist between IL-2 dose and arrhythmias. Elevations of the cardiac enzymes in plasma may precede the onset of arrhythmias and are not associated with ischemic vascular disease (155,359). A reduction in LVEF may be evident. Vasopressor support, mechanical ventilation, or antiarrhythmic therapy is often required during the course of treatment, but symptoms generally resolve rapidly after discontinuation of the drug (155,156,363).

Trastuzumab

Trastuzumab (Herceptin) is a humanized monoclonal antibody that targets the HER2 receptor. Although the exact mechanism is unclear, trastuzumab has been associated with cardiotoxicity in 4–7% of patients when used as a single agent (364,365). Trastuzumab cardiotoxicity is additive and synergistic when given in combination therapy (366,367). When the drug is administered with paclitaxel, toxicity has developed in 11% (10 of 91 patients), whereas CHF developed in only 1% of patients with paclitaxel alone (368). The risk of toxicity increases further when trastuzumab is administered with an anthracycline. In a phase III study of individuals with metastatic breast cancer, patients were randomized to doxorubicin alone or in combination with trastuzumab. Heart failure developed in only 6% of patients treated with the single agent, versus 27% of those on the combination arm (367,369). Most patients in whom heart failure develops achieve symptomatic relief with discontinuation of the agent and appropriate medical management. Patients should be encouraged to undergo long-term follow-up for potential delayed toxicity, which is common to anthracycline toxicity. Caution should be used when administering trastuzumab to women with prior cardiac dysfunction.

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MANAGEMENT OF ADVANCED HEART FAILURE

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MICHAEL W. RICH

> Dropsy is usually produced when a patient remains for a long time with impurities of the body following a long illness. The flesh is consumed and becomes water . . . The abdomen fills with fluid; the feet and legs swell; the shoulders, clavicles, chest and thighs melt away. If you begin treatment at the beginning, before the accumulation of water becomes excessive, you must administer purgatives which evacuate water or phlegm...the regimen of food, drink, exercise and walking will be until the patient becomes thin and dry, but only until the flesh becomes as strong as possible. This illness is fatal, above all through the progression of ascites. [Regardless of cause] the treatment is similar, but few survive. —Hippocrates

This description, written long ago, provides an interesting and insightful historical picture of the clinical syndrome and management of heart failure (1). However, the later stages of this disease remain strikingly similar to those described by Hippocrates despite remarkable advances in our understanding of heart failure pathophysiology, cardiac diagnostics, and therapeutic modalities. The accumulated knowledge has left several notable voids: The majority of the management strategies have excluded patients with the most advanced stages of the disease, and end-of-life issues have not been adequately studied. This chapter defines heart failure as a public health crisis by virtue of its prevalence, incidence, cost, morbidity, and mortality. The rationale for heart failure therapy is outlined, and standard pharmacotherapeutic approaches are described. Comprehensive outpatient care strategies are reviewed and linked to palliative care. Newer heart failure treatments, including biventricular pacemakers, surgical techniques to improve cardiac performance, and mechanical ventricular assist devices, likely transcend the definition of palliative care and are beyond the scope of this chapter.

EPIDEMIOLOGY

The management of systolic and diastolic cardiac dysfunction remains a clinical challenge for primary care physicians and cardiovascular specialists. Heart failure is the only cardiovascular disease that is increasing in prevalence. Nearly 5 million Americans have heart failure, and approximately 550,000 new cases are diagnosed annually (2). The annual incidence of heart failure in the United States is expected to exceed 800,000 by the year 2010 (3). The etiology of this “epidemic” is multifactorial but can largely be attributed to the aging U.S. population and advances in the early diagnosis and treatment of other cardiovascular diseases, particularly acute myocardial infarction. Heart failure affects 1% of individuals in their fifth decade of life but nearly 10% of the octogenarian population (2). Frequent and recurrent hospitalizations are common. The 90-day readmission rate following an index heart failure hospitalization ranges between 36% and 57% (4,5 and 6). The cost of managing these patients has been estimated as high as $38 billion annually, with nearly 60% spent on inpatient care (7).

PATHOPHYSIOLOGY

The heart must perform two mechanical functions to provide adequate blood flow throughout the body: It relaxes to allow the ventricular chambers to fill and contracts to eject the blood into the peripheral vasculature. Heart failure may result from abnormalities of either left ventricular (LV) relaxation (diastolic dysfunction) or contraction (systolic dysfunction). Coronary artery disease accounts for the majority of systolic heart failure (8). Other important etiologies include hypertension, chronic valvular heart disease (particularly chronic mitral and aortic regurgitation), and other nonischemic cardiomyopathies, including idiopathic dilated cardiomyopathy, heritable cardiomyopathies, and alcoholic cardiomyopathy. Approximately 40% of cases are attributable to diastolic dysfunction (9). The prevalence of diastolic heart failure is higher in the elderly and is commonly associated with hypertension and LV hypertrophy, obesity, diabetes, ischemic heart disease, and infiltrative diseases such as amyloidosis. Familial hypertrophic cardiomyopathies also result in diastolic dysfunction. Although the. annual mortality from diastolic heart failure is lower than that associated with systolic heart failure, the symptoms, exercise limitations, and hospitalization rates are similar to those experienced by patients with systolic dysfunction (10).

PROGNOSIS

The two primary modes of death in heart failure are progressive pump failure and cardiac arrhythmias. The frequency of these events correlates with symptom severity. Patients with New York Heart Association (NYHA) functional class II–III symptoms (Table 30-1) are more likely to die of an arrhythmia, whereas those with class IV symptoms more frequently die of progressive pump failure (11). Etiology, ejection fraction (EF, a measure of systolic function), hemodynamic parameters, neurohormone levels, exercise performance, and symptom severity also influence prognosis and management (12,13,14,15,16,17 and 18). Arguably the most convenient tool for clinical use is the NYHA functional classification, which can be readily determined from a carefully obtained history (Table 30-1). The annualized mortality risk can be estimated using the NYHA classification and ranges from 5% to 50% depending on the symptom severity. These data are concordant with the Framingham Heart Study, which demonstrated a 1- and 5-year heart failure mortality of 43% and 75% in men and 36% and 62% in women (25). These mortality risks, which are higher than most forms of cancer, highlight the importance of end-of-life planning for patients with advanced heart failure (26) (Fig. 30-1).

NYHA class	Definition	Annualized mortality without therapy (references)
I	Evidence of left ventricular dysfunction but capable of performing all levels of exertion	5–10% (19,20)
II	Comfortable at rest and with normal exertion; vigorous exertion causes excessive fatigue, dyspnea, chest pain, or palpitations	10–15% (21–23; DIG, unpublished results)
III	Comfortable at rest, but limited activity results in symptoms	15–20% (21–23; DIG, unpublished results)
IV	Symptomatic at rest; symptoms worsen with minimal activity	50% (24)

DIG, Digitalis Investigation Group; NYHA, New York Heart Association.

TABLE 30-1. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATIONS

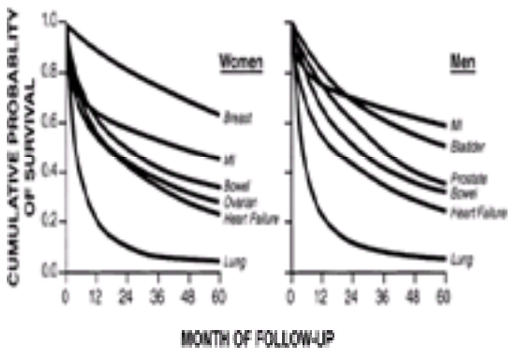

FIGURE 30-1. The 5-year survival rates of men and women with malignancy, myocardial infarction (MI), and heart failure. (Reprinted from Stewart S, MacIntyre K, Hole DJ, et al. More “malignant” than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Failure 2001;3:315–322, with permission.)

END-OF-LIFE CARE: STUDY TO UNDERSTAND PROGNOSES AND PREFERENCES FOR OUTCOMES AND RISKS OF TREATMENTS (SUPPORT) TRIAL

Physicians and patients are less likely to discuss end-of-life issues in heart failure than in other serious illnesses, such as the acquired immunodeficiency syndrome and cancer (27). This may result from the perception that heart failure is more “treatable” than malignant disease. Further, the clinical course of heart failure negatively impacts end-of-life discussions (28) (Fig. 30-2). The terminal phase of malignant disease is typically heralded by failure of aggressive treatment modalities and a significant functional decline, at which point a philosophical change from aggressive therapies to palliation is contemplated. Heart failure produces a gradual decline in functional capacity, punctuated by symptomatic exacerbations that often result in hospitalization. Timing the implementation of palliative care practices in this setting is more difficult. The SUPPORT trial demonstrated the challenges of predicting heart failure mortality. More than half of the patients with heart failure who died in SUPPORT had a predicted 6-month survival that exceeded 50%, even 3 days before death (29).

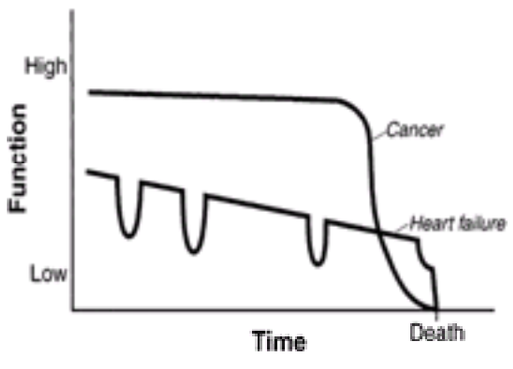

FIGURE 30-2. The clinical course of patients with cancer and heart failure. Individuals with malignancies often maintain a relatively high functional level until the disease progresses despite therapy. Heart failure is characterized by a slow functional decline punctuated by symptomatic exacerbations. (Redrawn from Lynn J. Serving patients who may die soon and their families: the role of hospice and other services. JAMA 2001;285:925–932, with permission.)

The SUPPORT trial provided meaningful insights into quality of life issues and the nature of treatment that was provided to 1404 patients with heart failure during the final months of life. Of these individuals, 38% died within the first year of follow-up. During the 6 months before death, patients experienced more daily activity dependencies and reduced activity levels but did not perceive a reduction in quality of life (29). These individuals remained capable of expressing their wishes, and pain relief and comfort care, rather than extension of life, became increasingly important. Twenty-three percent of the patients preferred to forgo resuscitation efforts (30). Only 25% reported this preference to their physician, and physicians incorrectly perceived the patients' wishes in 24% of cases. As death became imminent, dyspnea, confusion, and severe pain were prominent symptoms (31). Cardiopulmonary resuscitation, mechanical ventilation, or feeding tube placement was performed in nearly 40% of patients during the final 3 days of life. Of the octogenarians with heart failure who died in SUPPORT, 65% expired in a hospital or nursing home. Only 3% of heart failure patients died with hospice care, compared with 10% of those with malignant disease.

HEART FAILURE PHARMACOTHERAPY

Rationale

Our current understanding of the pathophysiology of heart failure is one of neurohormonal activation in response to cardiac injury or reduced cardiac output (32,33). Neurohormone activation is initially an adaptive response that is intended to improve cardiac output and maintain blood pressure and organ perfusion. However, chronic activation of the renin-angiotensin system and the sympathetic nervous system causes progressive LV dilation and further deterioration in cardiac performance. The current approach to heart failure pharmacotherapy is focused on inhibition of the deleterious effects of angiotensin II and norepinephrine on the heart and vasculature. Several other neurohormones and small peptides are maladaptively regulated in heart failure, and the effects of altering these substances are under investigation.

Overview

Table 30-2 provides a guide to the pharmacotherapy of systolic heart failure (EF £40%). The standard regimen includes an angiotensin-converting enzyme (ACE) inhibitor, b-adrenergic antagonist, digoxin, a loop diuretic, and spironolactone if the patient has NYHA class III–IV symptoms (34). Because several comorbid diseases may accompany heart failure, the treatment must be individualized, taking into consideration the complexity and cost of the medical regimen, tolerability, potential drug interactions, and compliance issues.

Agent(s)	NYHA functional class			
	I	II	III	IV
ACE inhibitors	+	+	+	+
Angiotensin II receptor blockers		+	+	
β-Adrenergic blockers	?+	+	+	?+
Spironolactone			+	+
Digoxin		+	+	+
Loop diuretics		+	+	+
Hydralazine/nitrates		+	+	?+
Positive inotropic agents				?+

ACE, angiotensin-converting enzyme; NYHA, New York Heart Association; +, agent(s) has demonstrated efficacy; ?+, fewer data support usage.

TABLE 30-2. MEDICAL THERAPY FOR SYSTOLIC HEART FAILURE

Angiotensin-Converting Enzyme Inhibitors

Activation of the renin-angiotensin pathway leads to accumulation of angiotensin II, a molecule with complex physiological actions, including vasoconstriction, salt and water retention, stimulation of thirst, and myocyte hypertrophy (35,36). ACE inhibitors prevent the production of angiotensin II via blockade of ACE. Numerous prospective, randomized clinical trials, involving more than 7000 patients with heart failure, have conclusively shown that ACE inhibitors slow disease progression, reduce hospitalizations, and decrease mortality (37). Importantly, ACE inhibitors provide these benefits across the symptomatic spectrum.

Angiotensin II Receptor Blockers

The angiotensin receptor blockers (ARBs) are a newer pharmaceutical class that inhibits the effects of angiotensin II by blocking its receptor. Inhibition at the receptor level theoretically provides more complete blockade, as non– ACE-dependent pathways also produce angiotensin II. Several clinical trials have evaluated the ARBs in heart failure. The second Evaluation of Losartan in the Elderly trial randomized 3152 patients ³60 years of age with an EF of <40% to receive either an ACE inhibitor (captopril) or an ARB (losartan) (38). Patients who received losartan had a similar 18-month survival to the captopril-treated group, and fewer permanent withdrawals occurred from losartan therapy. In the Valsartan Heart Failure trial, the combination of an ACE inhibitor and an ARB (valsartan) was compared to an ACE inhibitor alone. Overall, combination therapy was associated with a 13% reduction in the composite end point of death, hospitalization, resuscitated sudden death, or the need for intravenous inotropic or vasodilator support (39). The benefits of using both an ARB and an ACE inhibitor were limited to patients who did not receive a b-blocker. Until more data are available regarding the efficacy of the ARBs in heart failure, ACE inhibitors should remain first-line therapy.

b-Adrenergic Blockers

b-Blockers have become standard of care for the treatment of systolic heart failure. The b_1-selective b-blockers bisoprolol and metoprolol succinate and the third-generation agent carvedilol, a nonselective b-blocker with a-blocking and antioxidant properties, have been shown to improve heart failure outcomes (11,40,41 and 42). The b-blocker trials have consistently demonstrated symptomatic improvements, increased EF, reduced hospitalizations, and decreased mortality. The addition of a b-blocker to an ACE inhibitor produces an incremental mortality risk reduction of approximately 35% in patients with heart failure. To date, the majority of patients who have been enrolled in the b-blocker trials have had moderate symptoms (classes II and III). One trial evaluated the use of carvedilol in patients with stable class IV symptoms and was terminated prematurely because the carvedilol-treated patients had a 35% mortality reduction compared to placebo (43).

Spironolactone

The potassium-sparing diuretic spironolactone or placebo was added to an ACE inhibitor and a loop diuretic in the Randomized Aldactone Evaluation study (44). Spironolactonetreated patients with class III–IV symptoms experienced a 30% relative mortality reduction during a mean follow-up period of 24 months. The survival advantage that was demonstrated with this agent has been attributed to aldosterone antagonism, another of the maladaptively up-regulated neurohormones.

Digoxin

Digoxin, the oldest heart failure pharmaceutical, is a useful adjunct when added to a regimen that includes an ACE inhibitor and a b-blocker. The Digitalis Investigation Group trial randomized 6800 patients with systolic heart failure to receive either digoxin or placebo in addition to an ACE inhibitor and a loop diuretic (45). Digoxin did not reduce mortality, but it did reduce all-cause and heart failure hospitalizations. Digoxin also decreases the likelihood of symptomatic decline (46,47).

Diuretics

Diuretics are a critical component of heart failure therapy. Maintaining normal intra- and extravascular volume improves symptoms and exercise performance and reduces the hospitalization risk. Loop diuretics affect a high-volume diuresis when administered at appropriate doses. The addition of metolazone to a loop diuretic may further increase urine output. Patients with mild heart failure (class I) may require little if any diuretic on a daily basis. These patients can be taught to adjust their diuretic dose based on changes in body weight and the signs and symptoms of volume overload.

Hydralazine and Nitrates

The combination of hydralazine and isosorbide dinitrate is superior to placebo and the a-antagonist prazosin in reducing heart failure mortality (22). Compared to ACE inhibitors, hydralazine and nitrates have a similar effect on exercise tolerance but a less potent impact on mortality (23). Hydralazine and nitrates do not interfere with established neurohormonal pathways and therefore fit less well into our current understanding of heart failure pathophysiology. Nonetheless, this combination remains useful in patients with significant renal insufficiency and in those who are intolerant of ACE inhibitors and ARBs.

Inotropic Therapy

The role of inotropic therapy, including the b-adrenergic agonists (e.g., dobutamine) and the phosphodiesterase inhibitors (e.g., amrinone, milrinone), in patients with heart failure remains controversial. These agents increase myocardial contractility and improve hemodynamics, often resulting in symptomatic improvement. However, clinical trials of nondigitalis inotropic agents have consistently demonstrated excess mortality in the treatment arm (48,49,50 and 51). Cardiac arrhythmias mediate much of the excess mortality and are independent of the specific agent administered (49,51,52). Despite these observations, inotropic agents are administered to patients with severe heart failure to provide symptomatic relief and reduce hospitalizations. Aside from digoxin, none of the currently available inotropic agents can be administered orally. Intravenous b-adrenergic agonists and phosphodiesterase inhibitors can both be used as intermittent or continuous infusions. Intermittent infusions provide symptomatic palliation in up to 40% of patients with class IV heart failure (53,54) and have been shown to reduce subsequent hospitalizations in observational studies (55). However, intermittent inotropic therapy has not been tested in a placebo-controlled trial. The observed benefits in these studies may result from frequent encounters with health care providers, more intensive education, and the use of diuretics when early signs of volume. overload are detected. Continuous infusions of inotropic drugs have been used as end-of-life therapy for patients who are in cardiogenic shock or who have severe hemodynamic compromise. Inotropes are also used to “bridge” patients to other advanced heart failure therapies, including mechanical ventricular support and cardiac transplantation.

MANAGEMENT OF DIASTOLIC DYSFUNCTION

Evidence-based guidelines have been established for the management of systolic heart failure, but similar recommendations for the treatment of diastolic dysfunction are lacking. A major contributor to this knowledge deficit has been the lack of an inexpensive noninvasive method to diagnose diastolic heart failure reliably. Echocardiographic diagnostic criteria have been proposed that rely on measurement of blood flow characteristics across the mitral valve. Patients with mild diastolic dysfunction have evidence of impaired early LV relaxation, whereas individuals with more severe diastolic dysfunction exhibit a pattern of “restrictive” LV filling. In these patients, LV pressure is elevated, and left atrial contraction contributes relatively little to ventricular filling (56).

The primary strategy for managing heart failure with preserved LV systolic function is treatment of the underlying disease, which is most frequently hypertension or ischemic heart disease. Patients with diastolic heart failure are characteristically intolerant of atrial fibrillation, making restoration and maintenance of sinus rhythm important. Measures to control intravascular volume include dietary sodium restriction and the liberal use of diuretics. At present, no drug therapy significantly improves the relaxation properties of the heart. The pharmacotherapy of diastolic heart failure is therefore targeted at slowing the heart rate, controlling blood pressure, relieving ischemia, and promoting regression of LV hypertrophy. ACE inhibitors, calcium channel blockers (particularly the nondihydropyridines), b-blockers, and ARBs are most commonly used (57). A single agent or a combination of drugs with differing mechanisms of action is initiated and titrated to achieve symptomatic improvement. The treatment of diastolic dysfunction is often challenging, as symptomatic improvement may remain elusive despite multidrug therapy.

ROLE OF DISEASE MANAGEMENT IN END-STAGE HEART DISEASE

The concepts that underlie disease management are similar to those of a hospice in that a multidisciplinary, comprehensive, patient-focused approach is taken to the delivery of medical care. Further, heart failure disease management programs may also manage comorbid conditions. Several notable differences between hospice and disease management are evident. The emphasis of disease management is placed on reduction of resource use through aggressive follow-up targeted at early symptom detection and treatment. Disease management uses an evidence-based approach to medical therapy, including medication titration, and promotes patient education regarding dietary and fluid restrictions, self-monitoring techniques, and medication compliance. To date, little emphasis has been placed on providing comfort or palliative care in the context of heart failure disease management programs.

Multiple disease management strategies have improved outpatient heart failure outcomes. These protocols are typically initiated during a hospitalization, a time when patients may be more receptive to learning about heart failure and its treatment. This is followed in the outpatient setting by a period of enhanced patient contact, either through a clinic or by telephone. The educational efforts continue during the early posthospitalization period and are supplemented by queries directed at eliciting signs and symptoms of early clinical decompensation. As the patient demonstrates clinical stability, the frequency of contacts decreases. If he or she requires an emergency

room visit or hospitalization for heart failure, the cycle of intensive monitoring begins again.

A large portion of the published experience with disease management is from observational studies using patients as their own historical controls. These studies have included small numbers of patients followed for relatively short periods of time (58). Although such trials have inherent potential biases, outcome improvements have been consistent (58) (Table 30-3).

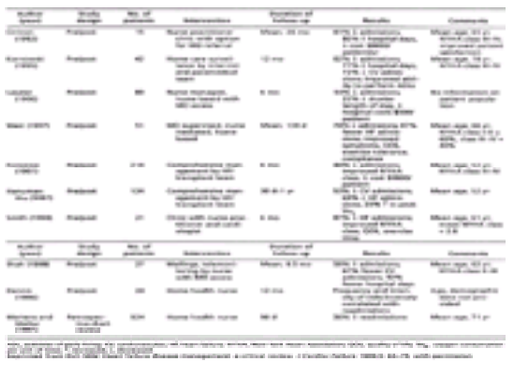

TABLE 30-3. NONRANDOMIZED TRIALS IN HEART FAILURE DISEASE MANAGEMENT

Fewer randomized trials of disease management have been published. Rich and associates (59) randomized 98 hospitalized geriatric patients to usual care or an intervention that included patient education, medication review, consultation with a social worker to expedite hospital discharge, dietary teaching, and close outpatient follow-up. Those who received the intervention had a 27% reduction in 90-day readmissions and fewer total hospital days than the usualcare group. A larger study using the same intervention randomized 282 patients and demonstrated a trend toward improvement in 90-day readmission-free survival in the intervention arm (60). The intervention decreased all-cause and heart failure readmissions, and fewer patients were readmitted multiple times. Quality of life measures improved more in the intervention group, and the cost of care was reduced by $460 per patient during this short follow-up period. Stewart and associates (61) studied 97 hospitalized patients who received predischarge education followed by a home visit 1 week later to assess patient knowledge and compliance and to detect clinical decompensation. Additional services and education were provided to those who demonstrated a knowledge deficit or noncompliance. Fewer intervention patients had unplanned hospitalizations, multiple readmissions, or out-of-hospital death. After 18 months, these patients experienced a nearly 50% reduction in the risk of hospitalization or out-of-hospital death (62).

Naylor et al. (63) evaluated comprehensive discharge planning in a geriatric population with heart failure or angina/myocardial infarction. The intervention included an assessment of patients' needs, patient and caregiver education, and coordination of postdischarge care. Nursing support was available by phone during the hospitalization and for 2 weeks following discharge. Patients who were randomized to the intervention had a 12% reduction in rehospitalizations. The effect of the intervention, however, was limited to the period during which the patient was being closely followed. To overcome this limitation, the period of observation was extended by adding outpatient services including home nursing visits and a prolonged period of contact in a broader population that included patients with heart failure (64). This intervention reduced 6-month readmissions by 45%, with fewer patients requiring multiple readmissions, fewer admissions related to the index hospitalization, and a significant reduction in hospital days per patient. The effects of improved access to primary care physicians was evaluated in a cohort of severely ill patients with heart failure, chronic lung disease, or diabetes in one of nine Veterans Administration Hospitals using an intervention that included patient education, discharge planning, and patient follow-up (65). This intervention resulted in a higher monthly readmission rate (0.19 vs. 0.14, $p = .005$), more hospital days per patient (10.2 vs. 8.8, $p = .041$), and no quality of life improvement.

Cline and associates (66) evaluated a disease management program focused on patient education and self-management techniques that provided access to a nurse-directed heart failure clinic for 1 year after an index admission. Mortality and quality of life did not differ between groups, but fewer readmissions and hospitalizations occurred in the intervention arm. Ekman and colleagues (67) described a nurse-monitored outpatient clinic that focused on early symptom detection, appropriate medical therapy, and education. This intervention did not improve symptoms, reduce readmissions, or alter the mortality (67). Jaarsma et al. (68) demonstrated that an intervention providing heart failure education in the hospital and at home during the week after discharge resulted in better self-care behaviors and a trend toward fewer readmissions. Finally, Serxner and associates (69) provided education to an outpatient population through serial mailings. This resulted in a heightened recognition of the importance of dietary sodium reduction as well as limitations in dietary sodium intake. Intervention patients were more compliant with diet, weight monitoring, and medications and were more confident in their ability to manage their disease. This intervention also resulted in greater improvements in perceived health status.

A meta-analysis of the randomized heart failure disease management trials did not demonstrate a mortality reduction with these strategies (70). Although most trials were unable to demonstrate a statistically significant reduction in hospitalizations, studies that used a multidisciplinary team approach consistently showed fewer hospitalizations, shorter hospital stays, reduced total hospital days, and fewer patients who required multiple readmissions. Only one of five trials demonstrated a positive impact on patientperceived quality of life, but seven of eight trials reported cost reductions in the intervention arm.

PALLIATIVE CARE IN HEART FAILURE

Little has been written about appropriate end-of-life care in heart failure. However, the severity of symptoms and the high morbidity and mortality that are associated with advanced heart failure support the application of palliative care principles to this disease.

Symptom relief is probably the most important palliative issue from the patient's perspective. Because heart failure symptoms vary from patient to patient, an individualized approach to pharmacotherapy is essential. Intra- and extravascular volume overload is a common problem that may manifest as exertional dyspnea, nocturnal dyspnea, abdominal fullness and discomfort, anorexia, and peripheral edema. Nonpharmacological management of volume overload should include daily weight monitoring and careful attention to dietary sodium and fluid intake. Food frequency questionnaires, completed by the patient or the caregivers (or both) provide important insights and facilitate targeted teaching. Patients should be instructed to report weight increases of more than 3–4 lb, as subtle weight increases often antedate worsening symptoms and are useful in directing diuretic therapy. Dietary sodium restriction is a critical component of fluid management. Patients should be counseled on a 2-g sodium diet, recognizing that many individuals are unable to achieve this level of dietary restraint consistently. Fluid restriction (2 liters/day) is valuable for some patients, particularly those with hyponatremia that may result from excess free water intake or the natriuretic effects of diuretics.

Flexible doses of loop diuretics (furosemide, torsemide, bumetanide) are the mainstay of the pharmacological management of excess volume. Patients who remain fluid overloaded despite standard diuretic doses should have the dose doubled, receive additional doses, or have metolazone added to the regimen. Augmented diuresis may be required for several days until the volume status returns to normal, at which time the baseline diuretic regimen can be resumed. Combination diuretic therapy should be used cautiously, as rapid reductions in intravascular volume (overdiuresis) and severe electrolyte abnormalities may occur. Patients who do not respond to an aggressive regimen of oral diuretics due to splanchnic congestion or poor absorption typically respond to intravenous diuretics. Nitrate preparations and morphine can also be used to improve dyspnea. Both agents are venodilators that reduce cardiac preload and pulmonary congestion. Morphine also has anxiolytic properties that are useful in acute or chronic dyspnea from heart failure.

Fatigue is a challenging heart failure symptom for patient and physician. The etiology of fatigue is multifactorial and may include insufficient cardiac output at rest and with activity, lactic acidosis (71), structural and functional changes in skeletal musculature (72,73 and 74), diminished respiratory reserve (75,76 and 77), impaired sleep, and depression (78,79). Fatigue that results from severe impairment of cardiac output may improve with inotropic support (80). Aerobic exercise, performed in formal or informal settings, improves exercise tolerance and decreases the physical limitations that are associated with advanced heart failure (81,82,83 and 84). Altered sleep patterns, including sleep-related breathing disorders and insomnia, are common in patients with heart failure and may contribute to fatigue (85).

Nausea and cachexia are common complaints in the later stages of heart failure. Nausea should prompt a thorough medication review to rule out an iatrogenic etiology. Right heart failure can cause nausea and may respond to enhanced diuresis. In some cases, antiemetics may be required for symptomatic relief. Heart failure–associated anorexia has been attributed to elevated circulating levels of tumor necrosis factor-a (86,87). Pharmacological blockade of tumor necrosis factor-aresults in improved cardiac remodeling and functional status, but there is currently no evidence to suggest that blockade of this pathway reverses anorexia or reduces mortality in humans (88).

ROLE OF THE HOSPICE IN HEART FAILURE CARE

The role of formal hospice programs in providing care to the advanced heart failure population has not been well studied. St. Christopher's Hospice in London reported the management of 19 heart failure patients with a mean age of 73 years (89). Common symptoms included weakness, breathlessness, drowsiness, and anorexia. Nonphysical needs included patient and family adjustments to dying, caregiver exhaustion, family psychological distress, and communication difficulties between the patient and family members or caregivers. The hospice provided psychosocial support, bereavement follow-up, and medication adjustments (principally analgesics and anxiolytics). Two patients required paracentesis for symptom relief. The authors concluded that palliative care specialists can provide an appropriate level of care to this population and that the needs of these patients are not significantly different from those of patients with malignancies. Hope Hospice of Florida has reported the results of managing seven patients with heart failure (90). Inpatient hospital days were reduced from 17.3 per 100 days to 0.66 per 100 days following enrollment into the hospice, and this was associated with a projected annual cost reduction of $45,680. Interestingly, local physicians were concerned that hospice referrals were being made “too soon,” but the 14- and 90-day mortality were 35% and 72%, respectively. A valuable innovation of this hospice was placing a “cardiac comfort care kit” in the home that included intravenous furosemide, nitroglycerin, morphine, anxiolytics, and antiemetics.

The National Hospice and Palliative Care Organization has outlined criteria to be used for patient enrollment to a hospice program (28). In addition to the general criteria that include the presence of a life-limiting illness, the patient's desire for comfort care, and documentation of disease progression and/or impaired nutritional status, cardiacspecific guidelines have been proposed. These guidelines include intractable or frequently recurrent heart failure with or without angina, the use of optimal medical management with diuretics and vasodilators, and the presence of concurrent factors that portend a poor prognosis, including symptomatic arrhythmias, a history of cardiac arrest or syncope, cardiogenic brain embolism, or concomitant human immunodeficiency viral disease.

CONCLUSIONS

Disease management and hospice programs appear to provide a suitable context for implementation of palliative care in advanced heart failure. Each brings unique perspectives, expertise, and management strategies that, if combined, could provide a comprehensive approach to the patient with end-stage heart failure. Disease management and hospice both emphasize education, self-care behaviors, and therapies targeted toward symptomatic improvement, all of which are concordant with the philosophy of palliative care. Disease management is heavily invested in the use of medical therapies that are documented to prolong survival and reduce hospitalization risk. Hospice is more focused on end-of-life issues, including relief of pain and anxiety and the use of community resources. The strengths of these strategies would be complementary and comprehensive. The role of aggressive treatments such as intravenous inotropic therapy in palliative care requires definition. The improvements in exercise performance that allow some patients to perform daily living activities with reductions in fatigue and dyspnea need to be balanced against increased risk of infection risk, which results from long-term intravenous access, high cost, and excess mortality. Other obstacles to the development of comprehensive end-of-life strategies for heart failure include the acceptance of these concepts by physicians who do not frequently use hospice programs, the consideration of new treatments and technologies that improve outcomes, and funding sources. Despite these barriers, the application of palliative care practices to patients with advanced heart failure is a logical extension of a field that is focused on providing quality and compassionate care to patients with terminal illnesses.

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31

MANAGEMENT OF HYPERCOAGULABLE STATES AND COAGULOPATHY

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Hemostasis is carefully balanced: Hemostatic plugs form at inappropriate openings in the vascular network, but thrombus extension is limited so that the remainder of the vascular highway remains fluid. Many disease processes can undermine this wondrous balance, either by inappropriate plugging of intact blood vessels, or by failure of hemostatic plug formation at sites of vascular wall breakdown. This chapter reviews clinical approaches to both pathological thrombosis and failure of hemostasis, with an eye toward practical measures in a palliative care setting.

THROMBOTIC DISORDERS

Thrombosis can be considered hemostasis that has gone wrong, occurring either at the wrong time or in the wrong place. This review mainly focuses on venous thromboembolic disease (VTE). Risk factors for the development of thrombosis are many, and the prevalence of thrombosis increases with disease severity. A high proportion of hospice patients are on warfarin sodium, reflecting the high rate of thrombotic complications (1). The presenting symptoms of some arterial thrombotic events and most venous events are vague. A high index of suspicion and specific testing for confirmation are required. Therapeutic intervention is undertaken with an understanding of the counterbalancing risks of thrombotic progression on the one hand, and hemorrhagic potential of anticoagulation on the other. Studies of the value of various diagnostic protocols, the efficacy and safety of specific acute interventions, and the risk of bleeding or recurrent thrombosis have led to the development of clinical pathways for diagnosis and have defined “acceptable” rates for complications such as bleeding and recurrent thrombosis. These studies have generally been conducted in patients with expected survival of 3 months or longer, and the principles defined in them may not fully translate to the palliative care setting. The physician must integrate acute care principles with specific end-of-life goals and expectations to arrive at an appropriate palliative care plan.

Mechanism Underlying Thrombotic Risk

Cancer is a well-established risk factor for VTE. The relationship was first reported by Trousseau in 1865 (2). Thrombosis is a major cause for morbidity in patients with neoplastic disease; the reported prevalence varies between 3.8% and 30.7% (3). Mechanisms of cancer-induced activation of the coagulation mechanism have been attributed to expression of tissue factor and cancer procoagulant factors on malignant cells and to inflammatory mechanisms (4,5). Proinflammatory cytokines such as tumor necrosis factor-aand interleukin-1b induce expression of tissue factor on endothelial cells (6). These mechanisms may explain why cancer patients are at increased risk for development of disseminated intravascular coagulation (DIC), which sometimes presents as localized thrombosis. Finally, chemotherapy, hormonal manipulations, and stasis resulting from vascular compression add to thrombotic risk (7).

Many other advanced disease states are also complicated by venous thrombosis. The incidence of stroke and venous thrombosis is as high as 4% in severe heart failure (8). Hepatic dysfunction increases risk of thrombosis, in part through decreased clearance of activated coagulation factors. Inflammatory reactions and acute phase response are common to many disease states; the actions of inflammatory cytokines and elevated levels of coagulation factor VIII, fibrinogen (9,10), and platelets all tip the balance toward thrombosis. Additional circumstantial risk factors include central venous catheters (4) and venous stasis associated with immobilization due to pain and debilitation.

Evaluation of the Patient with Venous Thrombosis

The spectrum of presenting signs and symptoms of VTE are often nonspecific. This problem may be particularly pronounced in the palliative care setting. Alternative explanations for extremity swelling include nonthrombotic vascular obstruction, heart failure, lymphatic obstruction, and neurological factors. Similarly, the sensation of breathlessness may stem from anxiety, cardiac failure, tumor invasion, infection, and obstructive pulmonary disease. Objective investigation is strongly recommended to establish an accurate diagnosis in patients in whom antithrombotic therapy would be considered (11).

Noninvasive studies are the diagnostic tools of choice, because contrast venography and pulmonary angiography (the reference standards) are inconvenient, costly, and associated with substantial morbidity. Quantitation of fibrin D-dimer (the plasmin-derived degradation product of cross-linked fibrin clot) is insufficient for exclusion of VTE in cancer patients. One study reported that the negative predictive value of the SimpliRED bedside D-dimer test was only 79% in cancer patients versus 97% in a more general population of ambulatory patients (12,13).

Clinical approaches that include noninvasive imaging studies are recommended for the evaluation of suspected VTE (14,15). Compression ultrasonography may be the best study for the diagnosis of proximal deep vein thrombosis in the terminal patient. It is simple, highly accurate, and fast when done in experienced facilities. The sensitivity for proximal leg deep vein thrombosis is reported at over 97%, but compression ultrasonography is significantly less useful in the evaluation of thrombosis below the knee (15).

Lung scintography has traditionally been the mainstay for noninvasive diagnosis of pulmonary embolism (PE). A “normal” report effectively excludes the diagnosis of PE, whereas a “high-probability” report is sufficient for diagnosis in a patient with a moderate to high clinical suspicion of PE (16). Unfortunately, approximately two-thirds of patients have a nondiagnostic lung scan (17). Pulmonary disease and tumor in the lung degrade the diagnostic yield of lung scans. Duplex ultrasound of the legs is positive in as many as half such patients, but a negative ultrasound does not exclude VTE in the patient in whom PE is clinically suspected (18). Recently, there has been considerable interest in spiral (helical) computed tomography (CT) for diagnosis. Spiral CT has a high sensitivity for detection of PE in central pulmonary vessels (sensitivity and positive predictive value approach 95%) (17). It may be particularly useful for uncovering alternative sources of pulmonary symptoms in patients with advanced disease, because the images also supply detail of the lung parenchyma, mediastinum, and pleura. The main concern about this promising technique is the lack of evidence for the safety of withholding anticoagulation therapy based on a negative spiral CT study. Other concerns include the low sensitivity for detection of embolism in subsegmental pulmonary arteries, the occasional misinterpretation of studies, the requirement for intravenous injection of a significant iodine-contrast dye load, and the high cost of the study (17,19).

Utilization of these diagnostic techniques in the palliative care setting has not been extensively evaluated. A survey of palliative care physicians in the United Kingdom revealed that only 60–80% of responding physicians would use tests to confirm a clinically suspected venous thrombotic event (20). One palliative care group's protocol for documentation of VTE was to establish the degree of clinical suspicion, and if high, to obtain leg ultrasonography. When PE is suspected and the leg ultrasound is inconclusive, spiral CT is obtained. Pulmonary scintography is reserved for patients in whom dye load is contraindicated (21).

Treatment of the Patient with Venous Thrombosis

The goals of treatment of VTE are to prevent death from progressive PE and to minimize the postphlebitic symptoms of pain, swelling, and dyspnea. The American College of Chest Physicians periodically updates its recommendations for the management of VTE in the nonpalliative care setting (22). Thrombolytic therapy would usually be considered an overly aggressive approach for the patient in such a setting. Anticoagulation is the mainstay of therapy. It is instituted immediately to inhibit new clot formation while the body's fibrinolytic mechanisms lyse clots and rechannelize obstructed blood vessels. Anticoagulation is then continued on a long-term basis to prevent recurrent thrombosis. The duration of anticoagulation therapy is stratified according to the patient's risk for recurrence.

The main complication of anticoagulation therapy is hemorrhage, and assessment of the risks of hemorrhage should be undertaken before instituting anticoagulation (Table 31-1). Absolute contraindications include significant active bleeding or presence of severe bleeding tendency. Relative contraindications include recent bleeding,

recent surgery, a moderate to severe degree of bleeding tendency, thrombocytopenia, active peptic ulcer disease, uncontrolled hypertension, and severe renal or liver disease. Central nervous system hemorrhage is a particular concern in patients with metastatic cancer in the brain, especially from melanoma, choriocarcinoma, or renal cell carcinoma. However, several authors advocate the safety of anticoagulation in the setting of nonhemorrhagic metastatic disease to the central nervous system when close control of anticoagulation is maintained (23,24). When hemorrhagic risk contraindicates anticoagulation therapy, or anticoagulation has proven insufficient to prevent thrombotic progression, inferior vena cava (IVC) filter devices can be deployed to preserve lung function and prevent death from acute PE.

Contraindications
Significant active bleeding (gastrointestinal or elsewhere)
Recent surgery or central nervous system procedure
Severe bleeding tendency
Factors conferring increased bleeding risk
Preexisting abnormality of hemostasis
Thrombocytopenia
Concomitant use of platelet-inhibiting drugs
Coagulopathy
Recent hemorrhagic episode
Recent major surgery
Comorbid disease states
Advanced disease
Active peptic ulcer disease
Uncontrolled hypertension
Severe renal or hepatic disease
Central nervous system metastasis
Heavy ethanol use
Advanced age

TABLE 31-1. CONTRAINDICATIONS AND RELATIVE RISK FACTORS FOR HEMORRHAGIC COMPLICATIONS OF ANTICOAGULANT THERAPY

Heparin drugs have been the mainstay of initial anticoagulation therapy owing to their immediate onset of action (25). Their anticoagulant effect is achieved by accelerating action of the plasma protein antithrombin. Heparin drugs have been subdivided into unfractionated heparin (UFH), and low-molecular-weight heparins (LMWH) derived by depolymerization of UFH. Synthetic pentasaccharide may soon join this group of anticoagulants (26).

Until recently, UFH has been the standard immediateacting anticoagulant used in the management of VTE. Its main advantages are low cost, short half-life, and reversibility by administration of protamine sulfate. The main disadvantages of UFH are its wide dose–response variability and narrow therapeutic window. Other complications include the need for parenteral administration, the rare but serious immunological condition *heparin-induced thrombocytopenia* (27), and the risk of osteoporosis with very-long-term heparin therapy (28). UFH is usually given by continuous infusion (29). The therapeutic dose is determined empirically. Algorithms for prescriptive dose adjustment are recommended based on frequent monitoring of anticoagulant effect (25). The sensitivity of the partial thromboplastin time (PTT) to heparin effect varies widely between labs; one should consult the local laboratory to learn the recommended therapeutic range. The PTT is a less useful yardstick of heparin effect in patients who have “heparin resistance,” which is defined as requirement of over 40,000 units of UFH/day to achieve a therapeutic range PTT (30). Either direct heparin assessment by “anti-factor Xa” assays (therapeutic range 0.35–0.70 U/ml) or a switch to LMWH is recommended in this setting.

LMWH preparations offer several important pharmacological advantages over the UFH precursor (31). LMWH is a parenteral medication, but depolymerization results in a longer half-life, greater bioavailability, and predictable pharmacodynamics. For the average patient with VTE, these pharmacological advantages translate into weight-adjusted dosing once or twice daily without a requirement for laboratory monitoring. These advantages also render LMWH an appropriate agent for outpatient use. Other potential advantages include reduced risk of bleeding (32,33), osteoporosis (28), and heparin-induced thrombocytopenia (34). The main disadvantages are increased cost and a prolonged anticoagulant effect that is less reversible with protamine sulfate. LMWH is cleared by the kidney; monitoring of levels is advisable in patients with renal insufficiency (creatinine greater than 2 mg/dl). Many large clinical trials have demonstrated that LMWH is equivalent in safety and efficacy to UFH in the management of acute VTE (35,36,37,38 and 39), and that it is safe to use in outpatient community-based care (40,41). Among cancer patients, no increased risk for recurrence of thrombosis was detected in LMWH study arms (42), although one study found a trend towards increased recurrence with once daily dosing of enoxaparin sodium compared to twice-daily dosing (43). Somewhat unexpectedly, metaanalysis revealed improved 3-month survival rates in cancer patients treated with LMWH (44,45). Multiple LMWH preparations are licensed. Dosing schedules for each preparation have been largely empirically determined, and they are not known to be interchangeable.

For patients requiring long-term anticoagulation to prevent recurrent thrombosis, warfarin sodium derivates (e.g., Coumadin) are frequently used (22). These oral vitamin K antagonists inhibit hepatic synthesis of multiple coagulation factors. The onset of oral anticoagulant effect is delayed until previously synthesized coagulation factors are cleared; “loading” doses do not overcome the long half-life of clotting factors. Because of this delay, oral anticoagulation is usually initiated concurrently with heparin drugs. Current recommendations suggest that heparin drugs be maintained for at least 5 days and continued for 2 days after laboratory studies confirm that adequate oral anticoagulation has been established.

Management of oral anticoagulation is complex due to the narrow therapeutic window, multiple drug interaction, inter-individual differences in hepatic metabolism, and shifting intensity of anticoagulation due to changes in oral intake (46). The therapeutic intensity of oral anticoagulation requires laboratory monitoring. A prothrombin time (PT)-based international normalized ratio (INR) target of 2.5 is suggested in most settings, but a higher target of 3.0 is suggested for patients with many types of mechanical heart valves (47). The typical initial dose of warfarin sodium is 5 mg/day in acute care patients, but initial doses may need to be lower in chronically ill patients, patients with poor nutrition, patients on medications that are known to increase oral anticoagulant effect, and in the elderly. Initially, INR monitoring and dose adjustment are done daily, with monitoring intervals increased as the chronic dose requirement is empirically established. Weekly evaluation may be prudent for at least the first 6–12 weeks of therapy, the time when the highest rate of hemorrhage occurs (48). In general patient populations, the risk of bleeding with INRs in the therapeutic range is reported between 2% and 3% (49), but cancer patients are at increased risk for bleeding complications. Adverse events might be avoided through more frequent monitoring (24,50). Outcome data are scant in the palliative care literature. One small hospice audit found a very high incidence of warfarin-related hemorrhagic events, and that external bleeding was quite distressing to the patients and their caregivers (1,51). Tight INR control was somewhat helpful, but required INR monitoring once every 2.4 days, adding a considerable burden to dying patients.

Management of a patient with an INR above the target value requires consideration of the degree of INR elevation and patient's risk of hemorrhage (Table 31-2). In patients who are not bleeding, dose adjustments may be sufficient. Low-dose oral vitamin K_1 can be used to shorten the period required for reestablishing the target level. In bleeding patients, the addition of coagulation factor replacement with fresh frozen plasma speeds correction of the INR (29,46). Bleeding patients that are unable to tolerate the volume load of plasma transfusion may be treated with prothrombincomplex concentrates (22) or recombinant factor VIIa; however, the complexity and expense of these measures should be carefully considered in the palliative care setting.

TABLE 31-2. GUIDELINES FOR REVERSAL OF WARFARIN SODIUM ANTICOAGULATION

LMWH has also been evaluated for the long-term anticoagulation of patients. The lack of monitoring requirements and absence of dietary or drug interactions offer significant advantages for the terminally ill patient. The dose chosen is generally similar to that used during initial anticoagulation therapy. Two long-term clinical trials (which included few cancer patients) suggested that prophylactic doses of LMWH may be effective (52,53).

Duration of anticoagulation is determined by risk of recurrence (22). Three to six months of anticoagulation is recommended for a patient with a reversible short-term risk factor, a minimum of 6 months for the patient with idiopathic VTE, and 12 months to indefinitely is recommended for the patient with a significant long-term risk factor. In terminally ill patients with persistent risk factors (such as cancer), the decision to continue anticoagulation should be regularly revisited, as it is unclear at what point the reduction in risk of thrombotic recurrence justifies the logistical burden and the ongoing risk of hemorrhage.

Recurrence of venous thrombosis in the face of anticoagulation appears to be a particular problem in patients with cancer or the antiphospholipid syndrome (14,54). A patient who develops thrombosis in the face of a subtherapeutic INR may be retreated with UFH or LMWH for 5–7 days and then be continued on warfarin sodium with the usual target INR of 2.5. For the patient who is already in the therapeutic INR range at the time of thrombosis, possible courses include aiming for a higher INR of 3 or switching to long-term LMWH. When risk of PE is high, IVC filter placement may be considered.

An IVC filter is not an alternative to anticoagulation, but placement of a filter may prolong life by prevention of acute PE. IVC filters reduce the short-term risk of PE, but

they do so at the expense of increased risk for progressive leg thrombosis and postphlebitic syndrome (55). Placement of an IVC filter should be reserved for patients with active bleeding or a high risk of bleeding, or for patients who develop recurrent thrombosis despite anticoagulant therapy. In the latter setting, concurrent anticoagulation should also be considered; thrombotic complications occurred in one-sixth of cancer patients who had a filter placed (23). Because of the expense and morbidity associated with IVC filters, their use in the palliative care setting should be carefully considered.

Catheter-Related Thromboses

Central catheters are commonly used in cancer and other chronically ill patients for administration of medications, transfusions, and blood monitoring. Thrombus may obstruct a line tip or form a sleeve around the intravascular portion of the catheter or obstruct the veins of the arm, neck, or mediastinum (56).

Low-dose thrombolytic therapy, instilled as a single dose (or occasionally as repeated doses), is usually effective in opening a tip thrombosis. Streptokinase, urokinase, and tissue plasminogen activator have been used for this purpose. Drug shortages have increased the use of tissue plasminogen activator for this purpose (57).

Vein thrombosis is a common complication of central lines. The incidence of symptomatic venous thrombosis is unclear. Symptoms of central vein thrombosis may be nonspecific and objective imaging is necessary to confirm the diagnosis. Anatomical limitations reduce the sensitivity of sonography, but the high specificity of sonography makes a positive study useful (56). Contrast venography may be useful in some patients. Optimal therapy of central vein thrombosis is uncertain. Full-dose anticoagulation or catheter removal may be sufficient, but if one approach is unsuccessful, both measures may be required (58,59). Open-label prospective randomized studies have shown utility of prophylaxis with very-low-dose (1 mg/day) warfarin sodium (60) or daily subcutaneous dalteparin sodium 2500 IU (61).

HEMORRHAGIC DISORDERS

Bleeding, especially if it is massive, can cause considerable anxiety for the patient, family, and health care providers (4). Bleeding may lead to debilitation from anemia and serve as a reminder of the uncontrolled and progressive course of illness. Patients may be unsettled by specific complications associated with bleeding in certain locations, such as chronic cough or dyspnea related to pulmonary bleeding. The clinical approach to these situations requires a balanced consideration of the underlying causes of bleeding (Table 31-3), the available therapeutic modalities, and the patient's palliative care goals.

Loss of vascular integrity
Tumor surface bleeding
Tumor erosion into a major vessel
Mucositis (stress, drug-related, acid-peptic disease, chemotherapy-induced, radiation-therapy induced)
Platelet defects
Thrombocytopenia
Marrow proliferative failure (myelophthisis, drug-induced, radiation therapy-induced, viral, vitamin deficiency)
Accelerated platelet clearance (disseminated intravascular coagulation, sepsis, immunologic, hypersplenism)
Platelet function defect (drug-induced, uremic, paraprotein effect)
Coagulation defects
Vitamin K deficiency (decreased intake or bowel flora production, malabsorption, oral anticoagulant-induced)
Liver disease
Disseminated intravascular coagulation
Accelerated fibrinolysis
Coagulation inhibitors (heparin drugs, autoimmune)
Interventional radiology (vascular embolization)

TABLE 31-3. MECHANISMS OF HEMORRHAGIC RISK

Mechanisms of Hemorrhagic Risk

Vascular Integrity

The loss of vascular wall integrity underlies all bleeding events. Multiple factors conspire in the terminally ill patient to destroy vascular integrity. Local tumor invasion in the gastrointestinal (GI) tract is associated with 12–17% of cases of GI hemorrhage in cancer patients (62). Chest wall breast carcinoma, endobronchial lung cancer, and locally invasive head and neck or cervical cancer can all cause local hemorrhage. Mucositis may be induced by nonsteroidal anti-inflammatory drugs, stress, peptic ulcer disease, local infection, or as a result of chemotherapy or radiation treatment. Finally, primary vascular defects may be involved, as in amyloidosis or vitamin C deficiency.

Platelet Function

Failure of hemostatic mechanisms may allow minor defects of vascular integrity to become manifest. Many factors can result in thrombocytopenia or diminished platelet function. Platelet counts above 50,000/mm^3 are generally well tolerated in the absence of trauma (63), and significant risk of spontaneous hemorrhage is rare until counts fall below 20,000/mm^3 (64). Failure of marrow production is a very common mechanism of thrombocytopenia. Extensive marrow replacement by tumor (myelophthisis) occurs early in leukemia, but is a sign of advanced metastatic disease in solid tumors. Other peripheral blood abnormalities lead to suspicion of myelophthisis, including pancytopenia and the presence of circulating neutrophil precursors, nucleated red blood cells, and “teardrop” red cells. Marrow failure is an anticipated complication of many antineoplastic drugs and may complicate radiation therapy. Other causes of marrow failure include vitamin deficiency (B_{12} or folate), hypothyroidism, viral infections, and adverse medication effects. If required, marrow failure can be confirmed by biopsy. Platelet-selective cytopenias and disorders characterized by shortened platelet survival are characteristic of some druginduced complications. Infection, DIC, hypersplenism, and autoimmune phenomena are all potential underlying mechanisms of thrombocytopenia. The approach to diagnosis and treatment of thrombocytopenia in the palliative care setting requires judgment as to potential benefits in relation to the discomfort, cost, and risk to the patient.

Medication-related inhibition of platelet function should be considered in the bleeding patient, as adjusting medications may be a relatively simple means of treating patients in the palliative care setting (65). Aspirin and most nonsteroidal anti-inflammatory drugs exert antiplatelet-effect due to potent cyclooxygenase inhibition. In addition, these agents increase the risk of gastric erosion. A burgeoning array of antiplatelet agents used in patients with vascular disease should also be questioned in the bleeding patient.

Coagulation Defects

Abnormalities of the coagulation mechanism such as vitamin K deficiency, hepatic disease, and DIC should be considered in a palliative care patient with bleeding (64).

Vitamin K is a fat-soluble factor required for hepatic synthesis of multiple coagulation proteins. Oral anticoagulants achieve their effect through inhibition of vitamin K metabolism. Nutritional deficiency of vitamin K occurs when there is impairment of either dietary intake or bowel flora synthesis of vitamin K. Disruption of both mechanisms is common (65). In addition, malabsorption disorders such as bowel resection/bypass, biliary obstruction, and use of cholestyramine may undermine fatsoluble vitamin absorption. Supportive laboratory evidence includes a prolonged prothrombin time (PT) with a normal or less prolonged activated partial thromboplastin time (aPTT) and normal fibrinogen and platelet levels. The PT should correct after 1:1 mixing with normal plasma, and the abnormalities should improve with vitamin K_1 administration.

Liver dysfunction contributes to bleeding in a variety of ways. The liver produces most coagulation proteins and is a reservoir for vitamin K. In addition to impaired synthetic capacity from parenchymal liver disease, liver dysfunction may cause portal hypertension with resulting thrombocytopenia from hypersplenism, and GI bleeding due to esophageal or rectal varices.

Owing to its short half-life, factor VII levels fall early in the course of liver disease, resulting in prolongation of the PT, which should correct on 1:1 mix with normal plasma. Mildly elevated fibrin degradation products may reflect defective hepatic clearance. The aPTT is typically less prolonged than the PT, and levels of fibrinogen and platelets are variable. Other clinical or biochemical evidence should support the diagnosis of hepatic disease. Clinical improvement in hemostasis with vitamin K_1 administration is generally limited.

DIC is a secondary coagulation disturbance associated with many disorders. There is a frequent association of DIC with cancer. Other causes include trauma, burns, sepsis, and prolonged circulatory insufficiency. DIC is characterized by activation of both procoagulant and fibrinolytic pathways. Activation of these pathways results in

consumption of platelets and coagulation factors, intravascular deposition of fibrin, and simultaneous release of fibrin degradation products and destabilization of hemostatic plugs (66). The thrombotic spectrum of DIC includes macrovascular thrombosis and microvascular obstruction with multiorgan failure. The hemorrhagic spectrum ranges from asymptomatic laboratory abnormalities to increased bruising, reoccurrence of bleeding at sites of prior trauma, or even apparently spontaneous mucosal bleeding. The diagnosis of DIC rests on clinical suspicion supported by laboratory abnormalities including prolonged PT and aPTT, decreased fibrinogen and platelets, and a positive test for fibrin split products or D-dimer.

Clinical Approaches to the Bleeding Patient

The nature and severity of bleeding and underlying cause define the spectrum of interventions available to the bleeding patient. The patient's anticipated life expectancy, quality of life, care setting, and palliative care goals may narrow the spectrum. One must balance the potential benefits of intervention (Table 31-4) with the consequences. In addition to general supportive measures, the care plan may entail avoidance of interventions that increase bleeding risk, local measures to treat bleeding, and systemic interventions to improve hemostasis.

General supportive measures
Identify the patient at risk
Establish open communication of issues for care
Generate care plan and revisit as required
Consider measures for catastrophic bleeding
Use of sedatives (midazolam hydrochloride)
Revisit as required by patient course
Local measures
Packing
Compressive dressings and postures
Topical hemostats (collagen, thrombin, fibrin gel, antifibrinolytics)
Topical astringents or vasoconstrictors (silver nitrate, alum, formaldehyde, cocaine, epinephrine)
Special techniques
Endoscopic interventions (cauterization, sclerosis, ligation)
Interventional radiology (vascular embolization)
Palliative radiotherapy
Palliative surgery (vascular ligation)
Systemic interventions
Discontinue antiplatelet and antithrombotic medications
Vitamin K
Antifibrinolytic medications (tranexamic acid, e-aminocaproic acid)
Transfusion support
Platelets or plasma for hemostasis
Red blood cells to treat anemia
Somatostatin analogs (octreotide acetate)

Modified from Regnard B, Mancini I, Pereira J, et al. Palliative management of bleeding events in advanced cancer patients. J Palliat Care 1998;14:50–54.

TABLE 31-4. PALLIATIVE MANAGEMENT OF THE BLEEDING PATIENT

General Supportive Measures

It is helpful to identify patients at particular risk for massive bleeding. Tumors likely to present bleeding problems include fungating tumors of the head and neck, gynecological tumors, and tumors close to major vessels. Patients on antithrombotic therapy and those with severe liver disease or marrow failure are also at increased risk for hemorrhage. Massive bleeding can be extremely distressing to patients and caregivers alike. Panic responses and calls to emergency medical personnel may result in the initiation of inappropriate interventions. Anticipatory conversations between patients and care provision teams empower caregivers to act appropriately if massive bleeding develops (67). Patients with hematemesis should be placed in the left lateral position to reduce respiratory compromise. Use of dark colored towels and basins helps make blood loss less evident, and thus reduces anxiety associated with bleeding. It may be helpful to have prefilled syringes containing sedative medication (e.g., 5 mg of midazolam hydrochloride) available for subcutaneous administration in the event of catastrophic hemorrhage (67,68).

Local Measures

Local interventions to control hemorrhage include compression dressings, application of materials to improve hemostasis, and special procedures to occlude bleeding vessels (64). Packing is useful in areas such as the nose, rectum, or vagina. Pressure through use of balloon catheters or posturing is of additional benefit in areas of small capillary or venous bleeding. Choice of topical agents to further improve hemostasis is generally based on local factors, cost, and individual considerations. Topical cocaine has been used with nasal packing.

Acetone may similarly improve the efficacy of vaginal packing. Purified gelatin, compressed packed foam (Gelfoam), and bovine-derived collagen provide surfaces for formation of a hemostatic clot. Bovine thrombin can be applied topically in powder form to dressings or directly onto oozing surfaces. It can also be used in solution to moisten dressings (69). Fibrin gel can be applied directly to bleeding surfaces (70). Aluminum astringents, such as 1% alum solution or 1 g of sucralfate tablet dispersed in water-soluble gel (e.g., K-Y jelly), can be applied to bleeding sites once or twice daily. Cauterizing and vasoconstrictive agents are alternative approaches to controlling hemorrhage. Formaldehyde solutions have been used to control hematuria (71), and may control bleeding associated with radiation proctitis (72,73). Silver nitrate cauterization is commonly used for nasal bleeding. Epinephrine (either alone in a 0.002% solution, or in combination with lidocaine) may be used to induce vasoconstriction. Lidocaine doses should not exceed 7 mg/kg when used in combination with epinephrine (74,75).

Special Techniques

Specific local interventions include endoscopic or intravascular application of hemostatic measures and use of radiotherapy to induce vascular sclerosis. The spectrum of endoscopic procedures includes cauterization and electrically induced coagulation (76), application of sclerosing agents and ligation of esophageal varices (77,78), and topical application of hemostatic agents. In addition to inconvenience, the risks of endoscopic procedures include worsened bleeding through physical trauma and perforation of organs. Vascular embolization by interventional radiology has been used for a variety of bleeding indications (64,79). Embolic particles include metal coils and gelatin sponge. The technique is restricted to vascular beds in which catheters can be easily guided. Vascular access is usually obtained via an axillary or femoral approach. Embolization therapy is well established in the treatment of head and neck, pelvic, and pulmonary neoplasm-associated bleeding. Complications include the need for mild sedation during the procedure, embolization of vascular beds not affected by tumor, bleeding at the site of vascular access, and a “postembolization” syndrome characterized by discomfort, malaise, and fever after vessel occlusion of a large tumor mass. Palliative radiation therapy may be used to control hemorrhage from head and neck, gynecological, GI, bladder, and other tumors (64,80). The optimal method of treatment remains controversial. Prior therapy in the same radiation field increases the risk of adverse events and limits the utility of this approach in some patients. (For further discussion of this area see Chapter 49.)

Systemic Interventions

Systemic interventions include augmentation of platelet or coagulation mechanisms and inhibition of fibrinolytic mechanisms. Alternatively, some medications may improve vascular or other responses to bleeding. Red blood cell transfusion may palliate the symptoms of anemia.

In the bleeding patient with a platelet count under 50,000/mm^3, platelet transfusion may temporarily help control bleeding. Prophylactic platelet transfusions are used in the care of patients with marrow failure and severe thrombocytopenia under 10,000/mm^3 to 20,000/mm^3 (81). Use of a 10,000/mm^3 threshold for prophylaxis appears to have similar safety to a 20,000/mm^3 threshold (81); however, bleeding may occur with platelet counts over 20,000/mm^3 when associated with vascular and anatomical abnormalities (82). Platelet transfusion therapy is complicated by the short survival of transfused platelets. Although the mean platelet life span is 9.5 days in normal individuals (83), platelet survival may be less than 3 days in patients with stable platelet counts near 20,000/mm^3 due to marrow hypoplasia (84). In the palliative setting marrow failure is often a chronic problem and a single platelet transfusion is unlikely to raise the platelet count for more then a few days. The limited role and complications associated with platelet transfusions should be discussed with the patient and the care providing team to arrive at an appropriate care plan. Palliation with limited platelet transfusions may be considered when symptoms of bleeding are distressing, including mucosal bleeding, painful hematomas, headache, and disturbed vision due to recent hemorrhage (85). (For more extensive comments see Chapter 67.)

The treatment of coagulopathy should be based on the underlying mechanism, the extent of coagulation disturbance, and the urgency of correction of the defect. Vitamin K deficiency and the effect of oral anticoagulation usually respond to vitamin K_1 within 24 hours. Vitamin K_1 is available as 5-mg oral tablets; subcutaneous administration is preferable in patients in whom malabsorption is a factor. Chronic administration (such as 5 mg twice per week) may be required to maintain the effect. Intravenous infusion is discouraged except in emergencies because of rare reports of anaphylactic reaction (86). For rapid correction of the coagulopathy of vitamin K deficiency, and treatment of bleeding patients with liver disease or malignancy-associated DIC, plasma transfusion support is the mainstay of therapy (65). Although fresh frozen plasma contains all necessary coagulation proteins, its use may be considered excessive in the palliative care setting, and supportive care is often limited to comfort measures. In DIC some have recommended use of heparin to control thrombin-generated consumption of platelets and coagulation factors, but its use in this setting remains controversial (64,65).

Antifibrinolytic agents prevent clot lysis by blocking the binding sites of plasmin and its activators in plasma. Among these agents, tranexamic acid is ten times more potent than e-aminocaproic acid and has a longer half-life (87). These drugs are rapidly absorbed from the GI tract and excreted in the urine, and both have dose-related nausea, vomiting, and diarrhea as their main toxicities. A dose of tranexamic acid of 1.5 g, followed by 1 g three times per day, or e-aminocaproic acid

started at 5 g, followed by 1 g four times per day, was used in one palliative care study (88). Fourteen of 16 patients had cessation of tumor-associated bleeding, with most having complete control of hemorrhage within 4 days. Treatment was continued for up to 54 days and bleeding was not reported after cessation of the therapy. Topical administration of these agents was described in this study and in several case reports (64,89). Although antifibrinolytic agents have been used in patients with thrombocytopenic bleeding, results of studies have not been consistent. One placebo-controlled trial did not demonstrate benefit in a population of patients with aplastic anemia or myelodysplasia (90), but two small studies with aminocaproic acid showed some effect on control of hemorrhage (87). Systemic antifibinolytic therapy increases the risk of thrombosis and should be used very cautiously in DIC.

Systemic interventions are occasionally used to alter the physiological response to bleeding. An example is the use of the somatostatin analog octreotide acetate in patients with GI bleeding (64). Although mostly used in the acute treatment of upper GI bleeding, at least one successful use in a palliative care setting is reported (67). It was suggested that octreotide acetate results in decreased splanchnic blood flow, reduced venous pressures, a cytoprotective effect, and suppression of gastric acid secretion. The recommended dose was 50–100 µg administered subcutaneously every 12 hours, increased according to clinical response to a maximum of 600 µg per day. Continuous infusion by either intravenous or subcutaneous route is a possible alternative (64).

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UROLOGIC ISSUES OF PALLIATIVE CARE

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The management of patients with a progressive medical disease should allow them to live the remainder of their lives to their fullest potential, maximizing both the quality and quantity of life. The development of complications related to the genitourinary system is not uncommon in these patients. Although some of these problems may merely be considered annoyances, others are quite serious and can potentially undermine the quality of life. The most serious complications can reduce life expectancy.

A common classification of urinary tract problems differentiates the urinary tract into upper and lower systems. The upper urinary tract refers to those organs proximal to the ureterovesical junction. The lower urinary tract pertains to the bladder, prostate, and urethra. This chapter discusses both the diagnosis and management of upper and lower urinary tract pathology.

OUTLET OBSTRUCTION

One of the most common problems originating from the urinary tract in men is bladder outlet obstruction, which can result from either benign or malignant processes. In men, the most common organ to obstruct the bladder is the prostate. Both men and women can develop bladder outlet obstruction from direct tumor extension or from other pathology originating from the rectum or urethra; a lesion of the ovary, cervix, or uterus may be the cause in women. The ultimate consequence to the patient with obstructive uropathy, without intervention, is renal failure secondary to chronic urinary retention. This condition progresses more rapidly if there is also underlying infection, a situation not uncommon in patients who fail to empty their bladder adequately.

A careful history may disclose the lesion responsible for urinary retention. Physiologically, failure to empty the bladder indicates failure to generate a detrusor pressure that is greater than the urethral resistance. This can either be from primary detrusor failure (e.g., associated with diabetes mellitus or sacral plexus injury) or from bladder outlet obstruction at or distal to the bladder neck. A detailed urologic history relating symptoms before the episode of urinary retention may clarify the underlying problem. Patients who complain of urinary frequency, urgency, nocturia, and a slow urinary stream frequently have obstruction as the underlying etiology of their urinary retention. In contrast, patients who report a slow stream, impaired bladder sensation, increasing intervals between voids, and decreased urgency are more likely to have primary detrusor failure (1). Because management of these two disorders differs significantly, it is obviously critical to make this distinction before initiating therapy.

Nonsurgical Treatment

Whereas the initial management of urinary retention secondary to benign prostatic hyperplasia (BPH) may warrant a period of catheter drainage and an empiric trial of selective a_1-blockers (terazosin hydrochloride, doxazosin mesylate, or tamsulosin hydrochloride), bladder outlet obstruction secondary to a malignant disease is unlikely to respond to this approach. Deconditioning and immobility are additional complicating factors in the terminally ill; debility in many terminally ill patients may decrease the likelihood for recovery of adequate bladder detrusor function. Those patients with BPH who fail initial conservative measures (a_1-blockers and bladder rest) after an adequate time period (e.g., 1–2 weeks) may be candidates for alternative measures. These other options, which are all invasive to an extent, include chronic urethral or suprapubic bladder drainage, intermittent catheterization, and surgical procedures, including urethral stenting or surgical resection of the obstructing tissue. In patients with malignant disease, these approaches can be considered earlier.

Hormonal Manipulation

A nonsurgical approach to patients with obstruction caused by prostate cancer involves hormonal manipulation. This approach should be especially considered for those patients not previously treated in this fashion. Up to 72% of patients with advanced prostate cancer may have symptoms of bladder outlet obstruction (2). In a 1989 review, Surya and Provet (3) suggested that androgen deprivation might be preferable to surgery as the initial mode of therapy. Androgen deprivation can either be in the form of surgical bilateral orchiectomy or “medical orchiectomy” with luteinizing hormone releasing hormone (LHRH) analogs (leuprolide or goserelin) or diethylstilbestrol. In those patients who are to be initiated on LHRH analogs, a recent bone scan should be available to rule out significant occult bony disease in the vertebral column. After starting therapy with LHRH analogs, a luteinizing hormone and consequent testosterone surge may occur within the first 2 weeks of therapy, and patients with significant vertebral metastases, whether occult or overt, are at significant risk for spinal cord compression. For similar reasons, patients with bone pain may have increased analgesic needs shortly after beginning treatment with LHRH analogs. To reduce the risk of these adverse events, the authors recommend that all patients should be started on an antiandrogen (flutamide, bicalutamide, nilutamide) before the initiation of LHRH agonist therapy to avoid the testosterone flare phenomenon. At a minimum, patients with documented bony disease in the cervical, thoracic, or lumbar axial skeleton should be started on an antiandrogen 7 days before initiating therapy with LHRH analogs. Two to three weeks after reduction of serum testosterone to castrate levels, patients who fail to void usually require surgical intervention or prolonged catheter drainage.

Clean Intermittent Catheterization

For the medically ill patient who does not wish to undergo a surgical procedure, or who is deemed medically unable to tolerate surgery, clean intermittent catheterization (CIC) and chronic indwelling catheterization represent the two most feasible options for adequate bladder decompression. These options are also best suited for those with retention secondary to detrusor failure as opposed to outlet obstruction. CIC has been the nonsurgical treatment of choice to empty the bladder since Lapides introduced the concept in the late 1960s (4). CIC enables a motivated patient to maintain freedom from a chronic indwelling catheter, thereby decreasing the attendant risks of infection, stricture, epididymitis, and symptoms associated with a defunctionalized bladder. Once a patient is placed on an adequate CIC schedule, bladder residuals must be monitored so that upper tract deterioration from storing urine at high pressures can be avoided. Common findings on routine urinalysis in those patients on CIC include pyuria and bacteriuria. In the absence of systemic evidence of infection (i.e., fever, flank pain, and leukocytosis), the use of broadspectrum antibiotics in an attempt to sterilize the urine should be avoided to forestall the development of resistant bacterial species (5). In patients with recurrent urosepsis, however, chronic antibiotic prophylaxis using low-dose antibiotics or urinary antiseptic drug regimens may be warranted. Sterile intermittent catheterization may also alleviate the problems of recurrent infections in those patients with clinical symptoms. Other issues that must be addressed before initiating CIC, especially in chronically ill patients, are sufficient manual dexterity and an adequate urethral channel to perform catheterization.

Indwelling Catheters

Although the use of indwelling catheters is usually limited to acute urinary retention, the benefits and risks of chronic catheterization in the medically ill patient must be carefully weighed. Frequently, a permanent urethral catheter is the most appropriate method of management in the patient with a very short life expectancy. Because

these catheters can be changed at longer intervals, they may also be the modality of choice for patients who are technically difficult to catheterize or are unable to catheterize themselves due to functional impairments. Urethral catheters are relatively simple devices, but may cause significant discomfort in those patients who experience bladder spasms. These patients may leak urine around the catheter and appear to be incontinent. Other problems with long-term catheterization include obstruction of urine drainage secondary to calcification of the catheter itself, calcification of the balloon, urethral stricture, urethritis, epididymitis, urosepsis, and urethral erosion. Although insertion of a suprapubic catheter avoids urethral trauma and irritation and decreases the risk of urosepsis, significant complications may still occur.

Surgical Treatment

Transurethral Resection of the Prostate

In patients who fail other treatments, transurethral resection of the prostate (TURP) remains the gold standard for the removal of obstructing tissue. Several newer techniques, however, have been developed for resecting, evaporating, or coagulating the obstructing prostatic tissue. These newer techniques include laser prostatectomy, electrosurgical vaporization of the prostate, transurethral needle ablation, and high-frequency radio wave ablation. All claim to have individual benefits to the patient beyond the standard TURP. However, all of these techniques are still evolving, and only several reports have recorded sustained efficacy. Follow-up in these studies is rarely longer than 2–3 years. Overall, these alternative methods have shown adequate subjective improvement in TURP, but objectively have been inferior. One comparison study of TURP and other less invasive therapies showed significantly lower recatheterization and lower readmission rates in TURP (6). It is also worthy of comment that all studies of less invasive therapies were in patients with symptomatic BPH and not obstructing cancer or overt urinary retention.

During a TURP, prostate tissue (benign or malignant) is removed (resected) using an electrocautery loop. Although the procedure itself is usually limited to 1 hour in length, the potential exists for the development of significant complications, especially in patients with underlying cardiac disease. TURP has the potential to create large fluid shifts by the absorption of irrigation fluid through venous channels during the resection. In a patient with underlying cardiac disease, this may place an otherwise compensated patient into congestive heart failure. Other risks associated with the procedure include bleeding, which has the potential to be significant during resection of a large gland; urinary tract infection; urethral stricture; dilutional hyponatremia; bladder perforation; erectile dysfunction; and urinary incontinence. The risk of urinary incontinence is a great concern when resecting malignant obstructing prostatic tissue, which causes alteration of the normal anatomical landmarks and may directly invade the external urethral sphincter.

Channel Transurethral Resection of the Prostate

An alternative to a standard TURP, in which all of the prostatic tissue is removed out to the surgical capsule, is the “channel” TURP. Channel TURP is defined as a TURP performed to alleviate obstructive voiding symptoms in the patient with advanced or previously treated cancer. It may also refer to a TURP performed to remove the obstructing tissue without necessarily removing all of the tissue to the surgical capsule. The advantage of channel TURP over the traditional TURP is that it is a more limited operation with less associated morbidity.

Mazur and Thompson (7) reviewed 41 patients with known prostate cancer who underwent channel TURP. All of these patients were able to void after the procedure, but 11 patients eventually required additional procedures at a minimum of 15 months after the initial resection. The only patients who were totally incontinent were those with invasion of the external sphincter who required intentional resection of this tissue to relieve the obstruction. Although not specifically detailed, the authors stated that there were no complications. Certainly, this duration of response represents a more than adequate period for most of our palliative care patients.

Urethral Stents

Recent advances with novel materials have led to the creation of self-expanding metal stents for placement into multiple organ systems, including the urinary tract. Several reports have suggested that these devices may be promising, especially for a patient with a limited life expectancy who wishes to remain free of catheters and external urine collection devices. Insertion of the stent itself is a relatively simple procedure and usually can be performed with local anesthesia and a minimal amount of sedation. Morgentaler and DeWolf (8) reviewed their experience with self-expanding prostatic stents in 25 patients with symptomatic bladder outlet obstruction. Twenty-one of the 25 patients were in urinary retention and the remaining four had either bladder neck contractures or severe symptoms of BPH. All patients underwent insertion of the Gianturco-Z stent (Cook Inc., Bloomington, IN). Initially, 95% of the patients were able to void. However, at longer follow-up, the success rate had declined to 75% due to stent migration in several patients. The authors theorized that the high rate of stent migration was due to improper selection of stent length. Additional studies (9,10 and 11) have evaluated different stents [UroLume Wallstent (American Medical Systems, Minnetonka, MN) and Titan intraprostatic stent]. The patients enrolled in these studies mainly suffered from BPH and not carcinoma. Overall, there was an almost 100% return of voiding function. Longer follow-up has shown that although these stents often need to be removed or replaced, symptomatic improvements are acceptable (12). The patients who failed to void were found to have detrusor failure secondary to chronic urinary retention. Symptoms after stent insertion were similar to those seen initially after TURP, namely urinary frequency, urgency, and hematuria. Failures in these studies were usually due to either improper stent length or migration of the stent. Complications were minor, and the patients who required stent removal were able to have it performed without extreme difficulty. Other studies, with small numbers of patients, have used stents in prostate cancer patients with similar short-term results (13). Thus, with improvement of stent sizing and insertion technique, intraprostatic stents hold significant promise for treating urinary outflow obstruction in the medically ill patient with bladder outlet obstruction.

IRRITATIVE VOIDING SYMPTOMS

The complex of irritative voiding symptoms refers to the symptoms of urinary frequency, urgency, and dysuria. These symptoms are common in patients seeking urologic evaluation. Rarely, they are the first indication of a severe underlying process. In addition to symptomatic relief, management must be aimed at identifying and treating the underlying disorder. Investigations may be warranted based on clinical presentation and patient prognosis.

Tumor-Related Symptoms

Although significantly less common than urinary tract infection, tumor invasion of the bladder can cause irritative bladder symptoms. Tumor invasion can originate from within the bladder, such as a transitional cell carcinoma, or from within the pelvis. A common genitourinary tumor that presents with irritative voiding symptoms is carcinoma *in situ* of the bladder. Common malignancies originating outside of the bladder include tumors of the ovary, os cervix, uterus, rectum, prostate, and colon.

The distinction between tumor invasion and urinary tract infection can usually be made on the basis of the history and several tests. Although symptoms are often similar, direct tumor invasion is more likely to have an insidious onset and gross hematuria (14). All patients with irritative voiding symptoms should undergo a detailed urinalysis (dipstick and microscopic analysis). If a urinary tract infection is excluded by urinalysis and urine culture (when indicated), other etiologies must be considered. The differential diagnosis for noninfectious causes of bladder irritability includes ureteral stones (secondary to irritation created by a calculus in the intramural tunnel), foreign bodies, and tumors. Like urinary tract infection, some of these diseases produce pyuria on routine urinalysis. However, unless there is a concurrent urinary tract infection, the urine should be sterile, except in the case of the sterile pyuria associated with genitourinary tuberculosis.

Any patient with new onset irritative voiding symptoms and sterile urine should have a voided urinary cytology. Although not necessarily diagnostic of a urothelial tumor, a positive urine cytology is particularly helpful in diagnosing carcinoma *in situ* of the bladder. However, a negative cytology does not exclude malignancy because this test is relatively insensitive for detecting low-grade superficial papillary transitional cell carcinomas of the bladder or upper tracts. These usually insidious tumors rarely cause any change in the normal voiding pattern. Other recent advances in the early diagnosis of carcinoma *in situ* include various urinary markers (e.g., NMP 22, BTA Stat), which are still under investigation as to their clinical usefulness. Although carcinoma *in situ* may be completely asymptomatic, it more commonly presents with irritative voiding symptoms.

Patients who develop irritative voiding symptoms associated with microscopic or gross hematuria and a negative urine also deserve additional evaluation. The gold standard for evaluating these patients includes an intravenous pyelogram and cystoscopy. In patients with an advanced medical illness, in whom diagnosis of a urothelial cancer may not change the overall management, this algorithm may be modified. Renal and bladder ultrasound, which can now be performed with relative ease, can detect solid tumors of the kidney or large tumors in the bladder; it would be unlikely, however, to diagnose a small tumor of the urothelium. Also, newer techniques in computed tomography (CT), with spiral scans and three-dimensional reconstruction, enable detailed evaluation of the entire urinary system with minimal morbidity. With the development of fiber optics and flexible cystoscopes, office or bedside cystoscopy can be performed with minimal discomfort and may be another alternative. If radiologic studies are unrevealing, cystoscopy may be required to rule out an irritative focus (e.g., tumor or stone within the bladder).

The initial treatment of a tumor that directly invades the bladder wall and causes irritative voiding symptoms should be transurethral resection of the bladder tumor (TURBT). Depending on the extent of the tumor, this can be carried out on an outpatient basis, although some form of anesthesia, usually spinal or general, is required. Transurethral resection entails using a special cystoscope (resectoscope) with a cutting “loop.” By application of an electrical current, the loop actually cuts the bladder tissue. This loop is used to resect the abnormal urothelium and the underlying layers (submucosa and muscularis) of the bladder. The diagnostic value of TURBT further supports its acceptance as the procedure of choice for the initial evaluation of all bladder tumors. If a full thickness biopsy is taken, the depth of invasion and the

degree of differentiation can be determined with a single procedure.

Patients who persist with disabling irritative voiding symptoms after TURBT may be treated symptomatically. The anticholinergic drugs oxybutynin chloride, tolterodine tartrate, and hyoscyamine (Ditropan, Detrol, Levsin SL, and Levsinex) are commonly used to treat urinary frequency, urgency, and nocturia. These drugs can be started at low doses and then titrated to effect. Caution must be used in those patients who also have a component of bladder outlet obstruction or bowel obstruction because their anticholinergic action may exacerbate urinary retention and gastrointestinal dysmotility. These patients require careful observation of voiding and bowel elimination patterns during treatment. Fortunately, there are more selective anticholinergic agents (e.g., tolterodine tartrate) now available that have fewer effects on gastrointestinal and parotid tissue and are therefore better tolerated. At times, a fine balance between irritative voiding symptoms and urinary retention can be obtained. In severe cases, anticholinergic therapy can be used to purposely induce retention and then the patient can be effectively managed with CIC as previously described. In addition, there is a relative contraindication to the use of anticholinergic therapy in patients with closed angle glaucoma. However, if patients maintain routine pharmacologic therapy for this condition, there should be little chance of clinical deterioration (15,16).

Urinary analgesic drugs, the most well known of which is phenazopyridine hydrochloride (Pyridium), may offer some symptomatic benefit to patients with irritative voiding symptoms. Phenazopyridine hydrochloride is converted from its inactive to its active form in the urinary tract. At times, a combination of this drug and an anticholinergic drug may be particularly helpful in relieving symptoms.

In rare cases, irritative voiding symptoms can be refractory to conservative therapies. If suffering from unrelieved symptoms is severe, urinary diversion may be contemplated. The standard form of urinary diversion with the lowest risk of short-term morbidity is the ileal conduit (see Radiation Cystitis). This procedure requires general anesthesia, major intraabdominal surgery, and a minimum 5- to 7-day postoperative recovery. Thus, although it is an alternative for those patients who have experienced a marked loss of independence and quality of life, the risks of the procedure itself must be weighed against the possible benefits.

Infection

Urinary tract infection is one of the most common conditions treated by physicians. Typical signs of lower urinary tract infection (simple cystitis) include urinary frequency, urgency, dysuria, foul smelling urine, hematuria, and suprapubic tenderness. Many cases of urinary tract infection in hospitalized or hospice patients are iatrogenic, secondary to urinary tract manipulation (most often by urethral catheters). When evaluating a patient who presents with acute onset of new irritative voiding symptoms, urinary tract infection should be first on the list of differential diagnoses. As previously mentioned, a urinalysis, including both dipstick and microscopic analysis, should be performed before starting empiric antibiotic therapy. Those patients who are either hospitalized, institutionalized, or who have recently been discharged from such a facility should also have a urine culture and sensitivity performed. The potential virulence of the bacterial flora associated with these facilities justifies this early culture. Likewise, a patient with recent urinary tract instrumentation including urethral catheterization who develops signs of urinary tract infection should also have a urine culture obtained at the initial evaluation.

When obtaining urine specimens from patients who appear to have failed appropriate antibiotic therapy, it is particularly important to ensure proper collection of the specimen. This especially holds true for debilitated patients and those with significant functional impairments, who may not be able to properly collect a clean-catch specimen. If the patient is unable to properly collect urine for urinalysis or urine culture, a catheterized specimen may be required before continuing or modifying treatment. Additionally, when specimens are collected from patients with either an indwelling catheter or condom catheter, one must take care in interpreting the results. Urine from these patients is almost always colonized with bacteria, and, consequently, the finding of bacteria on urinalysis does not necessarily indicate active urinary tract infection, although a negative culture under these circumstances is often considered adequate to rule out infection.

Patients who develop recurrent or relapsing symptomatic infections should undergo further evaluation to rule out a structural abnormality as the fundamental problem. Obstruction and stasis of urine flow at any level of the urinary tract predisposes to urinary infection. Obstruction can either be secondary to an anatomical abnormality, an obstructing stone or neoplasm, or bladder outlet obstruction. Factors contributing to urinary tract infection include diabetes mellitus and immunosuppression caused by cancer or its therapies. Other patients at risk include those on chronic steroid therapy and those infected with the human immunodeficiency virus.

Initial evaluation of patients with recurrent urinary tract infections should include a measurement of a “postvoid” residual to rule out the presence of a large residual urine. This can be performed by catheterizing a patient once he has voided to completion. As an alternative, the postvoid residual may be measured by ultrasound, which should include measurements of bladder volume both before and after voiding. Additional studies can include renal or bladder ultrasound to exclude hydronephrosis, noncontrast CT scan for stones, hydronephrosis, or diverticula, or intravenous pyelogram (IVP) to image the entire collecting system. Urine culture and sensitivity are mandatory when infections do not resolve with empiric antibiotic therapy.

Radiation Cystitis

It is not uncommon for patients to develop irritative voiding symptoms after external beam or interstitial radiation therapy to the pelvis. Radiation therapy is commonly used to treat genitourinary, gynecologic, and gastrointestinal tumors. Acute radiation cystitis after external beam radiation is characterized by dysuria, frequency, nocturia, and rarely, hematuria (17). Dean and Lytton (18) evaluated patients after pelvic irradiation and found that 21% reported urologic symptoms. However, in only 2.5% were these truly related to the radiation itself; in most cases, the symptoms were attributable to recurrent or persistent tumor.

Symptoms usually begin to develop after exposure to 3000 cGy, and there is an increased incidence of cystitis in those patients receiving greater than 6000–6500 cGy. Patients who experience persistent symptoms after completion of radiation fall into the category of chronic radiation cystitis. Open bladder surgery, in the subset of patients who receive higher doses of radiation, appears to be an independent risk factor for the development of chronic radiation cystitis.

Measures used to treat acute radiation cystitis are determined by the associated symptom complex. To address symptoms, drugs such as phenazopyridine hydrochloride or anticholinergics, either alone or in combination, are frequently administered. However, those patients who are refractory to these symptomatic treatments can become debilitated and experience a marked decline in quality of life due to severe urinary frequency, urgency, dysuria, nocturia, and at times, urge incontinence. Approaches to treating patients with such intense symptoms are limited to procedures that divert the urine stream. Occasionally, diversion of the urine by a Foley catheter (Bard Medical, Covington, GA) improves symptoms, although frequently the bladder discomfort is actually exacerbated by Foley balloon irritation. Alternatives to catheter drainage, which have been used with limited success, include small suprapubic tubes and bilateral percutaneous nephrostomies.

Invasive approaches aimed at diverting the urine or enlarging the bladder exist, but require major abdominal surgery. A potential contraindication to any surgery involving the bladder in patients with radiation cystitis is the effect of the extensive radiation itself. The risk of complications during or after augmentation cystoplasty or urinary diversion is increased in patients with irradiated bowel or bladder due an underlying vasculitis.

Augmentation cystoplasty involves enlarging the bladder by surgically creating a patch of either small bowel, colon, or stomach and attaching this to the dome of the bladder. Urinary diversion requires constructing either a urostomy with external appliance or continent diversion by creating a pouch that can be catheterized. Again, this procedure requires use of segments of small bowel or large bowel, both of which may have been irradiated. If urinary diversion is entertained, the bladder itself does not necessarily need to be removed. In fact, cystectomy should probably be avoided due to the increased surgical risks after radiation therapy. Although surgical diversion is considered in this discussion for completeness, few patients within the palliative care population are actually candidates for this intervention due to the associated surgical risks and time required for complete recuperation.

Chemical Cystitis

Several agents that are administered intravesically for the treatment of either superficial or multifocal transitional cell carcinoma of the bladder or carcinoma *in situ* can be potentially toxic and irritating. All of these agents have the potential to cause a chemical cystitis to varying degrees.

The most common and most effective medication used for intravesical treatment of bladder carcinoma is bacillus Calmette-Guérin (BCG). A standard course of BCG therapy involves weekly bladder instillations for 6 weeks. Depending on the clinical response and physician preference, maintenance therapy may continue after the initial 6- week regimen. Symptoms of urinary frequency, dysuria, and hematuria usually develop after 2 or 3 instillations and may last for approximately 2 days after each treatment. These symptoms are an expected consequence of the immune stimulation and inflammatory reaction that are thought to be essential components of the mechanism of action of BCG (19). Lamm et al. (20) reviewed the complications of BCG therapy in 1278 patients and found that 91% developed dysuria, 90% had urinary frequency, and 43% had hematuria. These symptoms seemed to increase with both the duration and frequency of treatments. Although BCG is available in several strains, the local irritative symptoms were not limited to any particular strain.

In patients undergoing a 6-week course of therapy, symptoms can usually be well controlled with the combination of phenazopyridine hydrochloride and anticholinergic medications. Although there have not been any randomized or controlled studies of these medications, several investigators with over 2600 patients support their routine use for symptomatic relief (21). For those patients refractory to this regimen, or in those patients who continue with maintenance therapy, treatment with isoniazid, diphenhydramine hydrochloride, acetaminophen, and nonsteroidal antiinflammatory medications can be helpful. Treatment is usually continued for the

duration of symptoms and may be given prophylactically for 3 days starting on the morning of BCG administration. Because all of these agents have a different mechanism of action, they are frequently used in combinations, and doses are titrated until a maximal effect is obtained. A rare complication of treatment with BCG is development of a nonfunctional contracted bladder, which occurs in approximately 0.2% of cases. Because contracted bladders did not develop in patients with severe irritative symptoms who were treated with prophylactic isoniazid, early treatment with antituberculous medication may help prevent this disabling complication.

Local irritative side effects are seen somewhat less frequently with other intravesical chemotherapeutic regimens. Agents used for intravesical treatment of bladder cancer include triethylenethiophosphoramide (Thiotepa), etoglucid (Epodyl), mitomycin C, doxorubicin, and INF-a. Mitomycin C has been associated with chemical cystitis in 10–15% of patients and, in rare cases, can lead to a contracted bladder. Doxorubicin has also been associated with chemical cystitis and defunctionalized bladders. Treatment of cystitis for these agents is similar to that of BCG except that antituberculous medications have no effect on irritative symptoms from these agents.

Systemic administration of some cytotoxic drugs can also lead to irritative symptoms. These symptoms are commonly associated with cyclophosphamide and ifosfamide (oxazaphosphorine alkylating agents), busulfan (1,4-dimethane-sulfonayoxybutane), and methenamine mandelate (22). These symptoms are avoided with these agents through the concomitant administration of mesna during chemotherapy. Mesna is a chelating agent that binds acrolein, a toxic byproduct of phosphamides, thereby decreasing its toxic effects.

HEMATURIA

General Considerations

Gross hematuria refers to blood in the urine that can be seen with the naked eye. It is important to confirm the presence of red blood cells in urine once dark urine is discovered. There are multiple causes of discolored urine other than blood within the specimen. Some of the more common causes of discolored urine include concentrated urine and systemic administration of flutamide, phenazopyridine hydrochloride, sulfasalazine, phenolphthalein (seen with the use of some over-the-counter laxatives), nitrofurantoin, metronidazole, methylene blue, and vitamin B complex.

Two commonly used methods of detecting blood in urine are the microscopic urinalysis and the urine dipstick test (UDT). The UDT works through a peroxidase reaction (i.e., the peroxidaselike activity of hemoglobin causes the oxidation of a chemical indicator impregnated within the dipstick and thereby changes its color). Intact red blood cells are not required for oxidation and false-positive readings may be caused by hemoglobinuria or myoglobinuria. Although the presence of intact red cells usually causes punctate discoloration of the dipstick rather than the uniform discoloration commonly seen with hemoglobinuria, confirmation of red cells is required. Therefore, all patients with a positive UDT require a microscopic urinalysis to confirm the presence of red blood cells. UDTs have been shown to have a sensitivity of greater than 90% when properly used (23,24 and 25). Although some controversy exists as to whether hematuria should be defined as 0–2 or 0–4/5 red blood cells per high power field, clearly more than 5 red blood cells per high power indicates the presence of blood.

Often, the location of urinary tract bleeding can be ascertained by careful history alone. The history should identify the presence or absence of pain, the color of the blood (bright red versus tea color versus light pink), the presence or absence of clots, and the timing of the presence of the hematuria in the urine stream. Also, hematuria must be differentiated from urethral bleeding, which usually presents as either blood at the meatus or spotting on the sheets or undergarments. Bright red blood usually implies that bleeding is from either the prostate or bladder, whereas darker blood more commonly originates from the upper urinary tract. Bleeding only on initiation of the urinary stream (initial hematuria) that is followed by clear urine implies that the bleeding originates distal to the level of the bladder neck or prostate. The presence of blood throughout the urine stream (total hematuria) usually implies that bleeding is from the kidney, ureter, or bladder, whereas terminal hematuria (blood mainly at the end of urination) again implies a disease process near either the bladder neck or prostatic urethra.

The evaluation of confirmed hematuria may include urine culture (in those patients with concurrent pyuria); voided or catheterized urine cytology; an imaging study to evaluate the kidneys, ureters, bladder, and urothelium; and cystoscopy to evaluate the urethra, prostate, and bladder urothelium. In patients with known urinary tract pathology, the assessment of patients with new onset hematuria may be modified, especially if previously performed studies have been negative. Because of the tendency of urothelial malignancies to recur, onset of hematuria within 6 months of initial evaluation should prompt consideration of repeating the above studies.

When considering which imaging study to obtain, the test that yields the most information and is considered the gold standard for imaging the entire urinary system is the IVP, although the IVP does have some limitations. If the ureters are unable to be visualized completely, additional studies may be warranted. Retrograde pyelography, which is used to identify lesions of the collecting system, may be performed at the time of cystoscopic evaluation to better evaluate or possibly localize upper urinary tract pathology.

Ultrasound can be considered as an alternative to IVP in patients at increased risk from exposure to contrast material, including those with azotemia, diabetes mellitus, or history of contrast allergy. Ultrasound is unable to visualize the collecting system unless it is significantly dilated and is not sensitive for detecting abnormalities of the urothelium. Real time ultrasound is relatively sensitive for detecting calcifications within the renal parenchyma and collecting system, but it does not clarify the clinical significance of such calcifications unless there is significant hydronephrosis, which, in turn, may depend in part on the hydrational status of the patient. If ultrasound is used, it should be coupled with a plain abdominal radiograph (a “kidney-ureter-bladder” film) to examine the remainder of the collecting system for calcifications that could lead to obstruction (e.g., ureteral calculus).

CT scans of the abdomen and pelvis have begun to take on a larger role in the screening evaluation for urologic pathology. CT scans are much more sensitive than IVP for detecting certain types of pathology (e.g., renal masses) although they may be less likely to detect subtle obstruction. With the now common use of spiral CT scanners, this technology is becoming more useful for obtaining large amounts of information in a short period of time. Spiral scanning allows not only narrow “cuts” through the kidney for the detection of stones less than 5 mm, but with newer software programs, three-dimensional reconstruction of the entire urinary tract with excellent detail. One benefit of IVP over CT is that it is a functional and dynamic study, which can be tailored to an individual patient when desired. During a CT scan, there is less control over the technique. Despite this drawback, spiral CT scans undoubtedly will hold a greater place in the imaging of the urinary system in the future.

Lower Tract Bleeding

Asymptomatic

Statistically, most microscopic hematuria of a urologic etiology is clinically asymptomatic and arises from the lower urinary tract. The most prevalent cause in males is BPH. Asymptomatic microscopic hematuria rarely, if ever, leads to a significant decrease in the hemoglobin or contributes to iron deficiency anemia. The significance of this microscopic hematuria lies in the fact that it may be a sign of occult urinary tract pathology. Most urologists believe that even a single detection of microscopic hematuria, without the evidence of infection or prior instrumentation, should be evaluated.

If the detection of urinary tract pathology is unlikely to alter the overall management of the patient, the standard algorithm for evaluating hematuria should be individualized. Cystoscopy is an invasive procedure and may be avoided if an obvious cause for the hematuria is detected. For example, if IVP or ultrasound demonstrate a large renal tumor, additional invasive procedures may not be necessary. Although it is possible that a patient could have a second malignancy or other bladder pathology (i.e., transitional cell carcinoma of the bladder), further evaluation may not necessarily be in the best interests of the patient.

If the source of microscopic hematuria is not detected by imaging studies and cystoscopy is contemplated, the benefits and risks of cystoscopy must be assessed. With newer flexible cystoscopes, cystoscopy now approaches both the risk and discomfort associated with urethral catheterization. However, both flexible and rigid cystoscopy can place a patient with well-compensated bladder outlet obstruction into urinary retention. Additionally, patients with BPH who are likely to have delicate dilated veins on the surface of the prostate as the etiology of their hematuria may be at risk for developing significant bleeding after this invasive procedure.

Asymptomatic gross hematuria can be managed similarly to microscopic hematuria. Patients who experience gross hematuria should be advised to increase their fluid intake and avoid strenuous activity. As long as the patient does not experience significant voiding difficulties, the evaluation of this disorder may proceed electively, in a similar fashion to that already described.

Symptomatic

Symptomatic hematuria is less common than asymptomatic hematuria, yet obviously more clinically significant. The spectrum of symptomatology in patients with gross hematuria ranges from no change in the voiding pattern to acute urinary retention caused by obstruction from clots. Most cases of gross hematuria are alarming, but relatively few patients actually require immediate intervention. As noted, patients with new onset gross hematuria should be told to avoid strenuous activities and increase fluid intake. Increased urine production may dilute the blood in the bladder and reduce the risk of forming clots. Patients taking antiplatelet medications should temporarily discontinue use of these agents because this may enhance the clotting process and limit additional bleeding. A patient is unlikely to develop significant voiding difficulties without the formation of blood clots. If clots are passed, significant bleeding should be assumed and the physician should anticipate the need for

intervention. As the concentration of blood increases and larger clots form, a patient eventually develops clot urinary retention.

The first step in treating a patient with clot urinary retention is to place a large catheter into the bladder and evacuate all of the clots. Preferably, a 22F or 24F catheter is used. It is nearly impossible to evacuate blood clots via 16F or 18F Foley catheters, which are commonly available in catheter kits, as it is not uncommon to irrigate 200–300 cc or more of clot from the bladder. It is also wise to insert a three-way Foley catheter, if available, so that continuous bladder irrigation (CBI) can be started if needed. Analogous to increasing the urine flow rate, CBI dilutes the concentration of blood in the urine, thereby helping to prevent new clot formation. After inserting the catheter and irrigating the bladder free of clot, the cause of the hematuria should be assessed, as described in the section General Considerations. In rare cases, when the bladder cannot be cleared of clot via an irrigating catheter, the patient may need operative intervention, with insertion of a resectoscope and manual clot evacuation with syringes or special equipment. In these patients, one should obtain a complete blood count and coagulation studies to exclude an underlying hematological problem. Unlike microscopic hematuria, gross hematuria can frequently lead to anemia and the hemoglobin must be followed. This is especially true of patients debilitated by chronic disease and those recently completing chemotherapy or radiation therapy, who may have decreased bone marrow reserves.

The management of patients who present with gross hematuria can usually be temporized with catheter drainage. Once imaging studies are performed, a differential diagnosis is formulated. When studies of the upper tracts are normal, the pathology is likely to reside either within the prostate or bladder. Cystoscopy should be able to establish the diagnosis and aid in the development of a treatment plan for disorders of either the prostate or bladder. If bleeding is discovered in the prostate during cystoscopy, it may be difficult to control with fulguration (electrocoagulation) alone. More commonly, when bleeding is discovered emanating from the prostate or bladder neck, some prostatic tissue needs to be resected, and the friable area requires coagulation. Bleeding in this area can be diffuse, and hemostasis may be achieved after completion of the procedure by placing a Foley catheter on traction, which causes compression and tamponade of vessels in the prostate and bladder neck. Once the acute situation is resolved, some patients may develop recurrent or chronic hematuria secondary to prostatic bleeding. There have been several reports indicating the efficacy of finasteride in these patients to decrease the extent and number of recurrent episodes of hematuria (26,27). It should be noted that all of these studies were performed on patients with BPH, and not prostate cancer. Despite this, finasteride is a generally well-tolerated medication and is often used empirically in this situation.

Bleeding that originates from within the bladder is termed *hemorrhagic cystitis* and, as already discussed, most commonly occurs from either radiation therapy or chemotherapeutic agents (14). Unlike radiation therapy, hematuria that results from chemotherapy drugs is not necessarily associated with irritative voiding symptoms. The chemotherapeutic agents most commonly associated with hemorrhagic cystitis are cyclophosphamide (Cytoxan) and its analogs. The incidence of hemorrhagic cystitis in early series was reported to be as high as 68%. The compound acrolein is the active metabolite that actually causes the bladder damage produced by cyclophosphamide (28,29). Mesna (2-mercaptoethane sulfonate) was developed specifically to bind to acrolein and thereby reduce the harmful effects of this by-product (30). Mesna is now given routinely when a patient is treated for malignancy with cyclophosphamide.

As described previously, the hematuria caused by radiation is commonly associated with dysuria, frequency, and urgency. Hemorrhagic cystitis can follow external beam or interstitial radiation treatment of primary genitourinary (prostate and bladder) malignancies, cancers of the cervix or rectum, or other pelvic lesions. The spectrum of hematuria secondary to radiation therapy also ranges from microscopic bleeding to bleeding severe enough to require transfusions. The time course of the development of hematuria ranges from months to years after the initiation of radiation therapy.

The damaging effects of radiation therapy on the bladder are similar to those found in other organs. The clinically significant symptoms in all organs are mediated through vascular damage. Radiation therapy induces an obliterative endarteritis, which leads to telangiectasias, submucosal hemorrhage, and fibrosis of smooth muscle and the interstitium. Ischemia of the mucosal surface due to this endarteritis produces areas of hypoxic tissue, which can break down and cause ulceration and bleeding. If chronic, these changes may eventuate in fibrosis (31). These derangements also cause an irradiated bladder to be extremely susceptible to injury and slow to heal when injured. Unlike treatment with cyclophosphamide, there are no prophylactic measures yet available that can be used to prevent bladder damage. Once radiation hemorrhagic cystitis occurs, aggressive symptomatic intervention should be initiated, and all further radiation exposure must be minimized.

As with other types of gross hematuria, initial management of radiation- or chemotherapy-induced cystitis involves insertion of a large Foley catheter. Removal of all clots is paramount for success in eventually clearing the urine. All subsequent therapies will work better in a bladder free of clots because clot evacuation reduces the naturally occurring fibrinolysins, which may act via the clotting cascade to actually perpetuate bleeding. If initial conservative management with catheter drainage and CBI fails, one must turn to alternative therapies to control the bleeding. Several topical agents can be applied intravesically to aid in cessation of bleeding. Before proceeding with these therapies, cystoscopy should be performed to rule out bleeding from the upper tracts and to fulgurate any obvious bleeding sites.

Empiric therapy may be initiated with e-aminocaproic acid (Amicar) given either orally, parenterally (32), or intravesically (33). e-aminocaproic acid reduces fibrinolysis by inhibiting plasminogen activator substances. This drug has been used extensively for idiopathic hematuria (34) and hematuria of unknown etiology associated with sickle cell disease (35,36). Although there have not been any controlled or randomized studies on the use of e-aminocaproic acid for treatment of hematuria, studies and clinical experience substantiate its use for severe hemorrhagic cystitis. Initially given either parenterally or orally, a loading dose of 5 g is followed by hourly doses of 1.00–1.25 g. Maximal response is usually achieved in 8–12 hours. Patients who initially respond to the parenteral route can then be changed to the oral route for maintenance therapy. Maintenance therapy includes taking the total daily dosage (6–8 g) and dividing it into four doses. When given intravesically, 200 mg of e-aminocaproic acid is added to each liter of 0.9% saline, and this mixture is administered as CBI. A side effect of e-aminocaproic acid is the formation of thick, tenacious clots, which can become difficult for the patient to pass spontaneously and extremely difficult to irrigate in patients with catheters. Administering e-aminocaproic acid to patients with bilateral upper tract bleeding is relatively contraindicated because thick clots in the renal pelvis or ureters can lead to upper tract obstruction, clot colic, or even renal failure.

Silver nitrate 0.5–1.0% mixed in sterile water may be administered into the bladder for treatment of acute bleeding. Rather than being run as CBI, this drug is instilled for 10–20 minutes, after which time the bladder is emptied. In certain refractory cases, multiple instillations may be required (37).

One percent alum has also shown some efficacy in treating hemorrhagic cystitis. Unlike silver nitrate, the 1% solution is usually given via CBI (38,39 and 40). Although somewhat effective, the rates of success are variable. The advantage of alum is that, apart from allergy, the substance is safe and requires no anesthesia.

The most efficacious and probably the most toxic treatment for hemorrhagic cystitis is intravesical formalin. Formalin is the aqueous solution of formaldehyde. Formalin acts by fixing the bladder mucosa by cross-linking proteins, thereby preventing necrosis, sloughing, and blood loss. Studies have shown formalin to be up to 80% effective in arresting bladder hemorrhage (41,42 and 43). Formalin is available as 37% or 40% aqueous formaldehyde, which is diluted with sterile water to yield final concentrations of 10% formalin (3.7% formaldehyde) or 1% formalin (0.37% formaldehyde). Formalin administration is painful and requires regional or general anesthesia. It is administered in concentrations ranging from 1.0–10%, starting at the lowest and progressing to the higher concentrations only as clinically indicated. The bladder is usually filled to capacity using gravity drainage and no more than 15 cm/H_2O pressure. Bladder instillation usually lasts 10–14 minutes (44).

Risks of formalin administration include damage to the bladder and upper tracts. Reflux of formalin to the kidneys can lead to fibrosis, obstruction, hydronephrosis, and papillary necrosis. A cystogram should be performed before formalin administration to rule out vesicoureteral reflux. In those patients who are shown to have reflux, ureteral balloon catheters may be inserted to prevent retrograde flow of formalin. Also, the procedure can be performed in the reverse Trendelenburg position to minimize reflux. Through its ability to cross-link proteins within the wall of the bladder, administration of formalin can lead to a decrease in bladder capacity and, in extreme cases, a nonfunctional, contracted bladder. Patients must be advised of these potential risks and formalin therapy must be reserved only for those cases of hemorrhagic cystitis which are truly refractory to all other medical treatments.

Two other nonsurgical therapies for hemorrhagic cystitis deserve mention. There have been several reports (45,46 and 47) on the use of hyperbaric oxygen therapy for radiationinduced hemorrhagic cystitis. More recent studies have now begun to report on some of the long-term success of the treatment (48,49). Hyperbaric oxygen induces hyperoxia, in which increased tissue concentrations of oxygen are attained by the increased dissolved oxygen in the serum. This condition results in neovascularization and secondary growth of healthy granulation tissue. Thus, hyperbaric oxygen tends to reverse the ischemic process caused by radiation therapy. Additionally, hyperoxia itself induces vasoconstriction, which may have a direct effect on bleeding from the bladder mucosa.

Finally, there have been some reports on the use of conjugated estrogens for treatment of hemorrhagic cystitis. Although the mechanism is unknown, there is a suggestion that estrogens may decrease capillary fragility. Liu et al. (50) reported on five consecutive cases in which bleeding from both radiation therapy and cyclophosphamide was successfully treated with conjugated estrogens. A follow-up study by Miller et al. (51) showed that six of seven patients treated with oral estrogens improved sufficiently to avoid further invasive therapy. Although no standard doses or length of therapy have been established, it appears that the usual starting dose of conjugated estrogens is 2.5 mg twice daily. After an adequate response has been achieved, the dose can be tapered. Final doses appear to be in the range of 1.25 mg daily, which can sometimes be weaned to 0.625 mg daily. Conjugated estrogens are well known to induce cardiovascular complications at high doses. Although no thromboembolic or cardiovascular complications occurred in the two studies mentioned, the long-term safety of estrogens at moderate to high doses is unknown. However, in a terminally ill patient, the benefits of estrogen therapy would certainly seem to outweigh the risks if it could control the significant bleeding associated with hemorrhagic cystitis.

For patients who do not respond to intravesical medical therapy, there are more invasive ways of decreasing bleeding from the bladder. Occasionally, selective embolization of branches of the hypogastric arteries is used to control bleeding. This therapy may be preferred in those terminally ill patients who can not undergo a

major surgical procedure because embolization can be performed under local anesthesia. The procedure works best when arteriography demonstrates a particular vessel responsible for the bleeding; unfortunately, this clinical scenario is unusual. If the entire bladder urothelium appears to be involved, the anterior branches of both hypogastric arteries may need to be occluded. Complications of embolization include claudication of the gluteal muscles, temporary lower extremity paralysis, and even necrosis of the bladder (52).

Some patients fail conservative measures and may require surgery to control the bleeding. Unfortunately, many of these patients are poor surgical candidates due to the ongoing hemorrhage and coagulopathy. These patients, who usually undergo urinary diversion, and at times cystectomy, universally do poorly.

Upper Tract Bleeding

Asymptomatic

As with bleeding from the lower urinary tract, asymptomatic bleeding from the upper tract rarely requires therapy and the same algorithm (i.e., urinalysis, imaging study, cystoscopy, and, possibly, culture) should be applied. Unlike asymptomatic bleeding from the lower urinary tract, however, imaging studies may be more useful than cystoscopy to determine the site of bleeding. For most patients with microscopic hematuria originating in the upper tracts, cystoscopy is usually normal. In patients with gross hematuria and no symptoms (gross painless hematuria), cystoscopy may be able to lateralize the bleeding if the study is performed while the patient is actively bleeding. Once the bladder is filled with irrigation fluid, a “jet” of blood may be seen emanating from the ureteral orifice on the side of the pathology.

Although bleeding itself does not necessarily warrant therapy, the pathology causing the bleeding may require treatment. Common etiologies for upper tract bleeding include renal masses, tumors of the renal pelvis and ureter, stones, and papillary necrosis. Once the site of the bleeding is determined either by imaging studies or cystoscopy, further diagnostic techniques, such as retrograde pyelography, selective ureteral catheterization for cytology, or ureteroscopy, can be entertained. The discussion of further therapy for each pathological condition in an asymptomatic patient is beyond the scope of this chapter.

Symptomatic

Symptomatic bleeding from the upper urinary tract is usually manifest by clot colic. *Clot colic* refers to the acute onset of flank pain secondary to acute ureteral obstruction. Clinically, clot colic mimics renal colic secondary to stones. Differentiating the two can sometimes be difficult, especially because clot colic in the presence of complete ureteral obstruction can present without overt hematuria.

The history and selective imaging studies may assist in the diagnosis of acute ureteral obstruction. Acute onset flank pain in an elderly person who has no history of kidney stones is more likely caused by clot or tumor. Likewise, upper urinary tract obstruction without evidence of calcifications on IVP or ultrasound is more likely secondary to clot or tumor.

Unlike bleeding from the lower urinary tract, there are only a few noninvasive measures that may benefit the patient with symptomatic upper tract bleeding. As in lower tract bleeding, forced diuresis by increasing oral and intravenous fluids may help dilute the blood in the urine sufficiently to prevent clot formation. The administration of e-aminocaproic acid can be considered, but as noted previously, upper tract bleeding is a relative contraindication for the use of this drug because small clots that could previously pass through the ureter may become large tenacious clots that can then obstruct the ureter. Thus, e-aminocaproic acid must be used judiciously in upper tract bleeding.

For patients who continue to develop clot colic from persistent upper urinary tract bleeding, most methods to stop the bleeding generally require invasive interventions. If no pathology is seen on imaging studies, including IVP or CT scan, an arteriogram may be warranted to exclude an arteriovenous fistula. This procedure may be able to identify the area of bleeding so that selective embolization can be performed.

If all studies, including the arteriogram, are normal, one may be faced with the difficult question of whether to remove a kidney or ureter. In this situation, cystoscopy may be extremely helpful in lateralizing the pathology. Once lateralized, ureteroscopy can often be employed as a diagnostic and even therapeutic tool. Recent advances in endoscopic equipment have enabled not only visualization of previously unreachable areas, but also biopsy and fulguration of any suspicious lesions. Despite these advances, there remain rare instances of highly symptomatic upper tract bleeding that are elusive to diagnosis. It is a particularly difficult decision to remove a kidney and ureter without a pathological diagnosis. In this situation, a patient must be very symptomatic and have failed all other more conservative means.

Patients with advanced renal cell carcinoma and metastatic disease may also develop bleeding and clot formation. Palliative measures may include radiation therapy or chemotherapy. Because the prognosis in these patients is very poor and surgery to remove the primary tumor does not impact positively on survival, it is again crucially important to document the degree of bleeding and the relative morbidity arising from the bleeding. Only when bleeding and clot colic impact negatively on quality of life should patients be considered for palliative nephrectomy. Statistically, metastatic tumors are much more likely than primary renal cell carcinomas in terminally ill patients.

UPPER TRACT OBSTRUCTION

Perhaps the most difficult problem in patients with advanced medical diseases is bilateral ureteral obstruction. Without treatment, these patients die of uremia. It is the physician's responsibility to help the patient make the appropriate decision concerning aggressive or conservative therapy. In patients with a limited life expectancy and poor quality of life, conservative therapy may allow a patient to die with dignity. Patients who have exhausted all primary treatments and cannot improve their functional status should not be considered for aggressive therapy. Patients who have received an adequate trial of all known useful therapy and who still have rapidly progressive ureteral obstruction despite the administration of optimal therapy will probably receive little benefit from urinary diversion. Also, patients with severe, unrelenting, and unmanageable pain are seldom better off after diversion.

Because the ultimate end point of bilateral ureteral obstruction is renal failure and uremia, both the patient and physician must understand that without treatment the condition is progressive. The progression of renal failure to uremia is marked by fatigue, decreased appetite, nausea, uremic coma, and eventually, death. In a patient who has been suffering with an end-stage malignancy, this may be a welcome situation.

Percutaneous Nephrostomy

Fortunately, with the advent of modern technology, those patients who are acceptable candidates for diversion of the urine stand a better chance of experiencing significant improvement with minimum morbidity. Before the 1970s, urinary diversion required an open surgical procedure to divert the flow of urine from the kidneys to the bladder. These procedures were problematic because most patients with malignant ureteral obstruction were poor surgical candidates due to their underlying nutritional, hematological, and immunologic status. Grabstald and McPhee (53) studied 218 patients who underwent open nephrostomy for malignant ureteral obstruction. They discovered a major life-threatening complication rate of 45%. There was a 3% operative mortality rate, and 43% of these patients did not leave the hospital. A later study by Meyer et al. (54) showed that 30% of patients undergoing an open urinary diversion procedure died within 52 days of surgery, and the overall median survival was only 3.3 months. Thus, open nephrostomy subjects the patient to significant operative and perioperative risks, without durable responses.

As a result of these outcomes, open surgical procedures have been supplanted by newer percutaneous techniques. In those patients who can tolerate anesthesia, cystoscopic insertion of ureteral stents is probably the preferred method of ureteral decompression. Relative contraindications to this procedure include hemodynamic instability and sepsis. When retrograde insertion of ureteral stents is unsuccessful, percutaneous nephrostomy is the technique of choice to relieve ureteral obstruction. As with most procedures, the chances of success and durable response depend mainly on the extent of the underlying disease and whether valid treatment options still exist. Some studies have shown a poor response after percutaneous nephrostomy. Keidan et al. (55) showed that although renal function improved in 85% of patients, the median survival was only 13 weeks, and 55% of the patients required additional hospitalizations for urosepsis and additional procedures. However, a study by Gasparini et al. (56) revealed much better results, albeit in a patient population that included many patients with newly diagnosed disease. They showed that 77% of patients undergoing either percutaneous nephrostomy (68%) or cystoscopic stent insertion (32%) were able to be discharged home. The mean survival time after urinary diversion was 75 weeks, and one patient lived as long as 4.7 years. There appeared to be a survival advantage in those patients who had not previously undergone hormonal therapy or chemotherapy. Also, in contrast to previous studies, there were no perioperative deaths or cardiac, pulmonary, or hemorrhagic complications. Thus, in properly selected patients, endoscopic or percutaneous urinary diversion can be relatively safe and efficacious.

A patient who successfully undergoes percutaneous nephrostomy and returns to a normal lifestyle can be considered for internalization of the nephrostomy tube. This requires placing a ureteral stent into the ureter through an anterograde approach. Hepperlen et al. (57) showed that patients with pigtail ureteral stents, whether inserted initially or after conversion of nephrostomy tube to stent, survived an average of 277 days. More importantly, these patients spent only 8.4% of their remaining time in the hospital. Similarly, Gibbons (58) found no operative mortalities and an 88% satisfaction rate after insertion of a ureteral stent. In contrast, a series by Brin et al. (59), which examined patient outcome after nephrostomy, revealed an average survival of 162 days with 63% of the time spent in the hospital. Thus, there appears

to be a significant survival and quality of life advantage in patients with indwelling stents compared to nephrostomy tubes.

Finally, as with urethral obstruction secondary to malignancy, there have been reports of self-expanding metal stents for treatment of ureteral obstruction. Lugmayr and Pauer (60) studied 23 patients who underwent insertion of the Wallstent device for malignant ureteral obstruction. They were successful in implanting the device in 97% of patients, and 83% of the stented ureters remained patent after 30 weeks. Because 81% of patients survived at least 6 months, the patency rate appeared comparable to survival rates. Thus, ureteral stenting may offer a viable option for treating the obstructed ureter.

PRIAPISM

Although an extremely uncommon oncologic complication, priapism can present severe morbidity for an affected patient. *Priapism* refers to a sustained, painful, penile erection not induced by sexual stimulation. If left untreated, priapism eventually leads to fibrosis and impotence. Although impotence is not generally a concern in the palliative care patient, the severe pain caused by priapism is certainly relevant. Priapism in the oncology patient may have multiple causes including vascular congestion from hematological malignancies, direct invasion of tumor into the corporal bodies, or disruption of venous outflow from a pelvic mass. Regardless of the cause, treatment of malignant priapism is aimed at treating the primary tumor and may include chemotherapy, radiation, or a combination of therapies (61).

CONCLUSION

The ultimate goal with all urologic complications in patients with progressive medical diseases is to maximize the quantity of life without jeopardizing or negatively impacting quality of life. Urologic complications in these patients can arise from benign or malignant disease processes, or as a consequence of treatments for an underlying malignancy. With the armamentarium of imaging studies, medications, and surgical interventions, the physician treating these patients can strive to allow them to live the remainder of their lives to their fullest capacity.

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33

MANAGEMENT OF RENAL FAILURE

SCOTT LONG

This chapter first describes renal failure (RF) in cancer patients at diagnosis and during treatment, mostly acute renal failure (ARF). The second part concerns the care of cancer patients dying of RF and for whom no curative therapy is sought.

RF is characterized by azotemia, metabolic offsets (e.g., hyperkalemia, acidosis), and, in many cases, volume overload. ARF is distinguished by an onset of serious dysfunction over a few days and is often reversible if treated early. Chronic renal failure (CRF) results from parenchymal damage of longer duration, sometimes evolving from undetected or uncorrectable ARF. No clearly defined time limit signals a patient's renal dysfunction passing from ARF to CRF. End-stage renal disease (ESRD) usually implies the need for dialysis to maintain acceptable quality of life in patients with CRF.

Although the perspective in this chapter is primarily medical, care of patients and families entails not only clinical expertise but also education, emotional support, guidance, patience, and responsibility at each step. This undertaking can rarely, if ever, be accomplished by a single clinician. Willing collaboration among caregivers with recognition of individual strengths and limitations furthers cooperation between those giving and those receiving care (1).

INCIDENCE AND CAUSES OF RENAL FAILURE IN CANCER PATIENTS

Epidemiology of RF has changed over recent decades (2,3,4 and 5). Older patients with significant comorbidity, wider use of nephrotoxic agents, increased incidence of sepsis, and multiorgan failure (3,4,6,7) have all complicated RF associated with malignancy. In one large study, one-third of patients with ARF were treated in intensive care units (ICU) in which mortality was 72% compared to mortality of 32% elsewhere in the hospital (8). Mortality rates of 40–60% in patients with ARF of all etiologies have shown little change over the last decades, although two surveys point out improved survival in ARF due to trauma, obstetric, and postoperative cases of severe ARF (3,5). Mortality rates in patients admitted to the hospital for ARF from the community are smaller (15–35%), especially when the kidney is the only organ compromised (9,10 and 11).

During the last two or three decades, ARF and other renal syndromes specifically related to cancer and its therapies have been reviewed (12,13,14,15,16,17,18,19,20,21 and 22). The literature does not set a single defining value of azotemia for ARF. Creatinine levels used to define ARF may vary from 2.0 to 5.7 mg/dl after rehydration, or as increases of 25–100% baseline in creatinine levels (2,5,20,23,24 and 25).

What is the incidence of RF among cancer patients? In a study of renal handling of morphine sulfate, 16 of 109 cancer patients had serum creatinine levels of 3 mg/dl or greater (26); in another study of 36 hospice patients with cancer, 10 had serum creatinine >1.35 mg/dl (27). RF is more common among patients with certain tumors (e.g., multiple myeloma, lymphomas) and treatments (e.g., bone marrow transplantation, radiocontrast dyes, aminoglycoside antibiotics). Among 494 myeloma patients with previously undiagnosed disease, 18% suffered from RF (creatinine >2 mg/dl) (23). In a particularly striking study, 80 of 85 myeloma patients presented with renal insufficiency (serum creatinine >1.5 mg/dl), with an average serum creatinine of 7.9 mg/dl (28). Of 349 patients with hematological neoplasms, 149 (43%) had serum creatinines above 1.7 mg/dl, and 43 (12%) required dialysis (29). Among 272 bone marrow transplant (BMT) patients, 64 (24%) required dialysis; 79 (29%) other patients doubled their baseline creatinines but did not require dialysis (30).

In cancer patients, RF may result from actions of tumors on the kidneys before treatment as well as from diagnostic and therapeutic procedures; nephrotoxicity and ischemia are the major pathways.

The most direct involvement of the kidneys by cancer is renal cell carcinoma (RCC). In one study, ARF occurred in 13% (33/259) of patients undergoing surgery for RCC. ARF was associated with solitary kidney, large tumor size, volume of renal tissue excised, longer times of ischemia, and *ex vivo* surgery (31). Although RF does not usually result from parenchymal infiltration and metastatic deposits, parenchymal infiltration by leukemias and lymphomas is commonly found at autopsy (15); renal metastases were found in 18% of autopsied cancer patients (32).

Acting at greater distance, tumors release antigens that may create pathological changes, most commonly membranous glomerulopathies (especially in stomach, colon, and lung cancer) and minimal change glomerulopathy (especially in Hodgkin's lymphomas). Reviews by Norris and by Mead and Morley are particularly concerned with glomerulopathies associated with cancer (18,33).

Tumor effects on the vascular system can produce RF through disseminated intravascular coagulation, hemolytic uremic syndrome (HUS), and thrombotic thrombocytopenic purpura (TTP); these may arise from distant tumors, from associated conditions like sepsis, and from therapies directed against cancer. Disseminated intravascular coagulation may occur from pancreatic, gastric, prostate, and trophoblastic tumors (33), as well as from acute promyelocytic leukemia (15). HUS and TTP may appear with mucinous gastric adenocarcinoma and carcinomas of pancreas and prostate. Lymphomatous vasculitis can produce glomerulopathy. Large-caliber vessels also may be involved, e.g., in renal vein thrombosis in RCC, in direct invasion by tumor, or in partial venous blockade by adenopathy. Some chemotherapeutic agents promote renal vasculopathy; for example, mitomycin C; bleomycin sulfate plus cisplatin; and high-dose cyclophosphamide plus radiation therapy all promote HUS and TTP.

A single type of tumor may compromise renal function through multiple pathways. Multiple myeloma produces renal damage by toxic effects of light-chain absorption in proximal tubular cells, by obstruction due to intratubular coagulation of myeloma proteins and cellular debris, by parenchymal precipitation of calcium phosphate crystals (nephrocalcinosis), and by deposition of amyloid (23,28).

Conditions blocking renal drainage promote ARF (e.g., retroperitoneal adenopathy of genitourinary tumors or lymphomas compressing ureters; intraureteral blockade by clots, by “sludge” of phosphates, urates, and other products of cell breakdown in tumor lysis syndrome or by renal stones). Retroperitoneal fibrosis producing RF may occur in some cancers after use of methysergide or as a late complication of radiation therapy (34). More distal bilateral ureteral obstruction by genitourinary or other pelvic tumors can produce the same deleterious effects.

Some chemotherapeutic and immunosuppressive agents create dose-related renal damage with such regularity that routine precautions are mandatory. Frequently used for solid tumors, cisplatin at 50–75 mg/m^2 lowers glomerular filtration and is directly toxic to renal cells. Presenting both acutely and chronically, its toxic effects can be mitigated by amifostine (35), in addition to using divided doses of cisplatin and to solute diuresis before, during, and after infusion of the agent. The related compound carboplatin creates less nephrotoxicity but significant marrow suppression; it can be helpful in patients with preexistent risk factors for RF.

Methotrexate (MTX), particularly at high doses (1–7 g/mg/m^2 body surface area), creates damage through intratubular obstruction by precipitated crystals and possibly through direct antimitotic effects on renal cells, as well as by afferent arteriolar constriction. Renal compromise before or after its first use calls for dose-adjustment of MTX; its toxicity includes not only the kidneys but also bone marrow and the gastrointestinal tract. Intravenous hydration with alkaline diuresis, especially if used with high doses requiring leukovorin, helps diminish this compound's nephrotoxicity. RF due to MTX often improves within weeks of its discontinuation (13,19,20 and 21).

Streptozotocin, used in endocrine tumors of the pancreas and in carcinoid tumors, causes both glomerular and proximal tubular damage, including renal insufficiency and, in some cases, severe ARF. RF after exposure to other alkylating agents (e.g., carmustine and lomustine) is less frequent but may present insidiously after

chemotherapy has finished (20,21).

Mitomycin C, used in gastric adenocarcinoma and bladder and anal cancers, produces thrombotic microangiopathy and HUS in patients receiving cumulative doses >30–50 mg/m^2. RF may result 1–2 months after the most recent dose or may be delayed for a much longer period. Although <10% of patients are afflicted with this complication, as many as one-third of these eventually require dialysis. Concurrent use of mitomycin C and tamoxifen citrate in breast cancer patients increases the risk of HUS (20).

The alkylating agent *ifosfamide* is associated with a wide range of renal toxicities. Young age, previous renal damage, and high doses are associated with RF, often delayed in appearance and at times irreversible. Use of divided doses protects the kidney. Mesna, used to prevent cystitis associated with ifosfamide, does not protect the kidney (36).

Among antineoplastic biological agents, *interleukin-2*, used in the treatment of melanoma and RCC, can cause serious renal compromise as part of changes mimicking sepsis, including hypotension and oliguric azotemia. Repeated use increases recurrence and severity of this syndrome. *Interferons* are less frequent causes of ARF (21).

The immunosuppressive agents, *cyclosporin A* and *FK306 (tacrolimus)*, produce both acute and chronic insults to renal function. Acute arteriolar vasoconstriction may be reversed by dose reduction and does not necessarily progress to ARF requiring dialysis. Chronic interstitial fibrosis can occur 6–12 months after exposure to these agents and can progress to ESRD (37,38).

BMT is increasingly used for hematological malignancies and solid tumors. Unfortunately, it is associated with ARF in one-third to one-half of patients. During marrow ablation and reduction of malignant cells, platinum compounds, high-dose MTX, and ifosfamide may precipitate tumor lysis syndrome, as may whole body irradiation. Infection, including sepsis with RF, may occur during this period of immunosuppression. ARF may be further favored by nephrotoxic compounds like aminoglycosides and amphotericin B, which are used to control infection. Infusion of marrow stored in dimethyl sulfoxide can reduce extracellular fluid (ECF) volume through nausea, vomiting, and diarrhea that has been triggered by chemotherapy. Short- and long-term renal injury due to whole body irradiation is reduced by shielding the kidneys (39). The incidence of many of these insults in BMT can be reduced by precautions such as i.v. hydration, alkaline diuresis, allopurinol, and leucopheresis. In the months after transplant, further serious RF can develop related to graft-versus-host disease and its therapies; still later, ARF associated with HUS/TTP may occur (20,38).

Other medications commonly used in cancer patients are also associated with ARF. Aminoglycosides and radiocontrast agents are nephrotoxic. Allergic interstitial nephritis leading to ARF has been identified with beta-lactam and sulfonamide antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics and furosemide, allopurinol, phenytoin, and cimetidine. Renal perfusion is reduced in some situations by NSAIDs, angiotensin converting enzyme inhibitors, calcineurin inhibitors, amphotericin B, interleukin-2, and radiocontrast dyes (40). Injury from radiocontrast agents is promoted by increased age (>60), diabetes mellitus, preexistent renal disease, decreased ECF volume, and high dose(s) of contrast. The recent use of acetylcysteine in patients with chronic renal insufficiency, as well as careful hydration before dye exposure in all patients, has increased renal protection from injury by radiocontrast dyes (41).

Chronic and acute comorbidities often exacerbate renal insult in cancer patients, many of whom are elderly with decreasing renal reserve and are burdened with other illnesses like diabetes mellitus. Age alone has been identified as an independent risk factor for RF in many studies (3,7,24), but not all (42,43,44 and 45). In the elderly, falling glomerular filtration rate, decreased muscle mass, and reduced ECF volume may produce a falsely “normal” creatinine, which overestimates real creatinine clearance. In this population, creatinine clearance should be measured for a more reliable guide to dosing of potential nephrotoxins (46). In ICUs, the chances of recovering meaningful life, or life at all, decrease rapidly as additional systems fail (5,11).

Anticipating and minimizing effects of disease and therapies on renal function are key steps in protecting one's patients from RF and reducing its complications. Even modest degrees of RF may increase mortality, independent of comorbidity (25). Iatrogenic RF was identified in 40–55% of patients with hospital-acquired renal insufficiency or failure (11,42,45). Many patients have two or more preexistent factors for renal damage, and >50% in one study had two or more acute insults (43,45). Evaluation of baseline renal function identifies patients already at risk, may signal the need for specific preventive measures, and guides treatment of evolving renal compromise if it arises.

DIAGNOSIS OF RENAL FAILURE

Rising azotemia in routine testing of asymptomatic patients is often the first indication of renal insufficiency or failure. Once alerted, the physician begins to search for causes, to measure the rate, and to correct the consequences of evolving failure. Much depends on early detection and effective treatment. ARF can evolve into death or into worsening RF and then CRF with or without dialysis (11,42,47,48). Preexistent renal compromise increases the risks of permanent renal damage (47). Delayed consultation (or no consultation) with nephrologists leads to worse outcomes for patients with RF (9,49).

Physiologically, ARF falls into three general categories: prerenal, renal [also called *parenchymal failure*, *intrinsic failure*, or *acute tubular necrosis* (ATN)], and postrenal. Most studies of ARF report hospital experience. Of 748 hospitalized patients with ARF of all etiologies, approximately 50% had ATN, 25% prerenal, 13% acute-on-chronic, and 10% postrenal causes (8). ATN predominates in the ICU. Community-based studies show greater incidence of prerenal and postrenal failure and lower incidence of ATN in patients hospitalized for community-acquired ARF (9,10 and 11). In each physiological category, RF is further characterized by urine output: anuric <50–100 ml/day, oliguric <400 ml/day, and nonoliguric at higher rates. Patients in nonoliguric RF generally fare better because volume overload is less problematic (11,24,43).

Prerenal failure indicates that one or more precipitating causes of failure are “upstream” from the kidney. A history of ECF depletion, decreases in daily weight and in fluid intake/output, and an examination revealing poor skin turgor, dry oral mucosa, dry axillae, resting tachycardia, orthostatic pulse and pressure, all suggest prerenal failure. Patients with prerenal failure tend to produce small amounts of concentrated urine with low sodium content. Creatinine (urine/plasma) ratios may be ³40, urinary osmolality ³500 mOsm/l, and fractional excretion of sodium £0.01 in patients without renal insufficiency and no recent diuretic use. Plasma blood urea nitrogen/creatinine in prerenal failure is usually ³20. These parameters are less reliable among elderly patients in whom the ability to concentrate urine is reduced (46). Urinary indices can be helpful but not diagnostic. In some patients, increased urine flow after cautious fluid challenge is diagnostic of prerenal failure; for example, small fluid challenges of 200 ml (plus or minus “renal” dopamine) with concomitant central venous or capillary wedge pressure measurement are helpful in assessing ECF status (50,51).

Urinary sediments in prerenal failure are generally free of cellular debris other than clear hyaline tubular casts. In ATN, “active” or “busy” sediments show epithelial cells, cellular debris, and tubular casts, but may contain no casts. Red cell casts suggest glomerulonephritis; tubular casts of leukocytes occur in allergic interstitial nephritis (e.g., due to penicillins, cephalosporins, NSAIDs, and allopurinol) (50,51).

Postrenal failure indicates obstruction “downstream” from the kidney. Ureteral obstruction by tumor, lymphadenopathy, or retroperitoneal fibrosis produces RF through increased back pressure, which compromises renal circulation and glomerular filtration and results in hypoxia. Renal vein thrombosis in renal cell carcinoma causes similar problems. Malignancy is a common cause of postrenal failure and is associated with higher death rates than obstruction of nonmalignant cause (52).

Identified prerenal or postrenal failure does not preclude parenchymal damage because ARF often has more than one cause (8,42,43,45,47). Laboratory testing can identify or consolidate a diagnosis of ATN. Imaging studies with ultrasound, computed tomography, and magnetic resonance imaging, often used early to rule out postobstructive lesions, also describe size and number of kidneys with estimation of cortical thickness to identify preexistent disease (53). Renal biopsy to guide therapy needs consideration if there are no obvious causes for parenchymal damage or if aspects of history, examination, and laboratory data suggest other causes of RF (e.g., glomerular, interstitial, or vascular disease) for which specific treatments exist. In large series of ARF of all etiologies, biopsy rates range from 0–24% (2,6,11,54). Some consider the presence of a terminal illness a contraindication for renal biopsy (55), although biopsy is frequent in workup of myeloma patients, ranging from 33–48% (28,56,57).

TREATMENT OF RENAL FAILURE

Therapies for RF in cancer patients can be divided into two groups, depending on clinical context. The first therapies (“cure plus care”) are based on the judgment that the quantity and quality of life at risk are worth great effort to save or prolong significantly. In this first group, therapy aims to correct underlying pathophysiology and its consequences and to optimize patients' health and comfort. The second group of therapies (“care only”) is brought into play when active curative therapy is no longer sought; these patients often continue some of the palliative measures (e.g., analgesia) started in the “cure plus care” phase. They receive comfort care through palliation of symptoms, understanding that such care will not reverse underlying disease but may make it easier to bear; at this point, hospice may become involved. During evolution of RF or cancer, placement of patients in these groups may change. Advance directives and other earlier consultations between patient/family and caregivers make further discussions easier for all concerned, even if earlier decisions are reversed (58,59).

Active treatment of some problems caused by RF may be required soon after detection to protect the patient's status during further workup and therapy and to prevent evolution of renal damage into long-lasting compromise or death. Treatments chosen depend on the severity of signs and symptoms, comorbidity, desired effects, side effects of each agent or intervention, and overall goals of patient and family.

Nondialytic Therapy

Volume overload most often occurs in patients with oliguric failure unresponsive to cautious fluid challenge. Diuretics (e.g., mannitol, furosemide) and vasodilators (e.g., lowdose dopamine) do not consistently convert oliguric to nonoliguric failure in the early phase of ARF (60,61). Medications to correct other aspects of ARF (e.g., sodium bicarbonate for acidosis or for urinary alkalinization) may promote volume overload and pulmonary edema. Oxygen should be used to counteract hypoxia in pulmonary edema. Increasing venous capacitance with morphine sulfate and some other vasodilators may gain time in the most urgent cases of volume overload. Pulmonary edema requires correction with hemodialysis or hemofiltration unless rapidly resolved by more conservative measures. In less urgent cases, restriction of salt (<2 g/day) and water (<1 l/day) intake, as well as loop diuretics in nonoliguric failure, protects patients from fluid overload. The gut also may be used to excrete fluid through the promotion of diarrhea with poorly reabsorbed carbohydrates like sorbitol or lactulose; as much as 4–5 l/day can be lost by these means.

Metabolic acidosis due to decreased acid excretion in RF and rising acid production in hypercatabolism exerts multiple deleterious effects (e.g., promotion of hyperkalemia and changes in protein structure and function). Neurological and cardiovascular deterioration may result. Acidosis can be controlled by oral or intravenous bicarbonate replacement to bring bicarbonate above 15 mEq/l. Monitoring protects patients from adverse consequences of bicarbonate loads, such as hypocalcemia, hypokalemia, alkalosis, and volume overload. In urgent cases, usually in conjunction with other metabolic offsets, acidosis requires dialysis (e.g., for bicarbonate <10 mEq/l or pH below 7.20). In less severe acidosis, diets low in protein (approximately 0.5 g/kg body weight/day) and high in carbohydrates (approximately 100 g/day) diminish acid production.

Hyperkalemia may accompany RF of all causes, but rapid accumulation of K^+ in ECF is especially threatening with tissue destruction (e.g., tumor lysis syndrome). Hyperkalemia and its treatment are best monitored with plasma levels and electrocardiographic changes. At [K^+] approximately 7 mEq/l, high T-waves and depressed S-T segments occur, followed at [K^+] approximately 8 mEq/l by intraventricular conduction blocks and loss of P-waves, leading to ventricular standstill. Emergent correction of hyperkalemia and follow-up measures to maintain plasma [K^+] at safe levels are described in standard medical texts and manuals.

Hypercalcemia (>14 mg/dl or 3.5 mmol/l, corrected for albumin) is a common metabolic emergency in cancer patients (62). Its incidence is as high as one-third of all myeloma patients with RF (16,56). Myeloma patients with serum [Ca^{2+}] >11.5 mg/dl (corrected for protein binding) had a significantly higher incidence of RF (49%) than those with lower [Ca^{2+}] (10%) (23). Of 50 patients seen for hypercalcemia in hospital setting, cancer was the cause in 41, half of these due to lung cancer (63). Further discussion of hypercalcemia and its treatment in cancer patients is found in Chapter 34.

Hyperuricemia (>15 mg/dl) in cancer patients is primarily the result of tumor lysis syndrome (16). In one series of 43 patients with hematological tumors, 26% were dialyzed for tumor lysis syndrome (29). In addition, tumor lysis syndrome occurs in patients with some solid tumors (64). It can occur spontaneously and should be sought before therapy in patients at risk. Diagnosis of acute uric acid nephropathy in tumor lysis syndrome is suggested by appropriate history and laboratory values. At uric acid levels >20 mg/dl, crystals form in the renal medulla to cause obstruction and inflammation promoting RF. Sludge of uric acid crystals and amorphous material in the renal pelvis and ureters may add a postrenal component. Urinary amorphous or crystalline urates are not diagnostic.

Prevention of hyperuricemia and other metabolic problems in tumor lysis syndrome is preferable to treatment whenever possible. Preventive measures given before, during, and after chemotherapy consist of vigorous intravenous hydration with loop diuretics, allopurinol, and, in patients not already hyperphosphatemic, urinary alkalinization. Alkalinization must be avoided in hyperphosphatemic patients because alkaline urine favors nephrocalcinosis and creates or worsens failure. Thiazide diuretics promote urate reabsorption and are not used. Even without sodium bicarbonate or acetazolamide, hydration may produce fluid overload, especially in oliguric RF. In such cases, hemodialysis is necessary, sometimes on a daily basis to reduce urate quickly.

Hyperphosphatemia (>5 mg/dl or >1.67 mmol/l), like hyperuricemia, is particularly threatening in tumor lysis syndrome. Not only is it associated with nephrocalcinosis, but concomitantly lowered [Ca^{2+}] may present problems in neuromuscular, cardiac, and central nervous system function. In severe cases, usually associated with other metabolic problems, hyperphosphatemia requires dialysis. Mild to moderate elevations of serum phosphate concentrations are commonly found in RF as a result of decreased renal phosphate clearance and increased release of cellular phosphates in acidosis. In these conditions, hyperphosphatemia usually is controlled by phosphate-binding antacids (e.g., aluminum hydroxide), by dietary reduction (including parenteral phosphate), and by avoidance of phosphate-rich enemas (e.g., Fleet enemas). Magnesium-containing antacid should not be used because magnesium accumulates in RF.

Infection in many patients precipitates RF, exacerbates established RF, and threatens renal recovery. Sepsis in patients with ARF is associated with increased mortality (2,3,11,29,54,56). Insults to body integrity are superimposed on the compromised immune system in RF by urinary catheters, intravascular devices, and intubation. During workup of a serious suspicion of infection, one should begin treatment with antibiotics that are chosen to minimize further renal damage and are adjusted for ARF and its concurrent therapies (e.g., dialysis) (65,66).

Some antibiotics can complicate RF. For example, penicillin G promotes seizure activity, whereas K^+ penicillin contributes to hyperkalemia (3 mEq/million units). Trimethoprim, cefoxitin sodium, and cefotetan disodium may cause spuriously high creatinine levels. Tetracyclines may promote uremia through their effects on protein metabolism. Antibiotics dependent on glomerular filtration and tubular secretion (e.g., penicillins, cephalosporins, trimethoprim, and sulfonamides) achieve higher urine concentrations than those dependent on glomerular filtration alone (e.g., aminoglycosides) and are often associated with allergic interstitial nephritis. The aminoglycosides are notoriously nephrotoxic (67).

Nutritional support is provided to patients with RF in partial compensation for protein catabolism and other metabolic dysfunctions, decreased intake, and nutrient loss (e.g., through dialysis). In patients with limited to moderate catabolism, patients should receive supplements to provide energy at 25–30 kcal/kg body weight/day. In those in severe hypercatabolic states (e.g., sepsis or multiple organ dysfunction), the target rates are nearer to 35 kcal/kg body weight/day because rates of oxygen consumption are 20–40% higher than those in normal health. In a prospective study, severe malnutrition was found in 130 of 309 patients with ARF; malnutrition showed a significant correlation with complications (e.g., sepsis), mortality, and length of stay. Of particular relevance to this chapter, 75 of these patients had cancer (68). Nonetheless, despite the many reasons aggressive nutritional supplementation should promote greater well-being and quicker healing in patients with ARF, clinical studies have not consistently shown better return of renal function and longer patient survival when it is provided (61,69).

For complicated patients in ICUs, nutritional supplements should start within 48–72 hours. Patients who are not expected to receive adequate calories by mouth within 5–6 days after onset of ARF should also start nutritional supplements. Enteral routes are preferred for physiological reasons, including the gut's barrier function, immune support, quality of life, and economy. Although dialysis may facilitate nutritional supplementation, it also imposes an additional route for nutrient loss, which will require replacement. Nutritional supplementation entails other risks, such as electrolyte and acid-base imbalances, and may require more intensive dialysis for control of volume and of increased uremia. For optimal nutritional support, the managing physician needs collaboration with a nephrologist, a nutritionist, a pharmacist, and nurses.

Hematological problems in RF include anemia and coagulation problems. *Anemia*, common even in early RF, often has several causes (e.g., bleeding, blood loss through dialysis or surgery, and diminished erythropoietin synthesis in damaged kidneys). Acute repletion occurs through hemostasis and transfusions; erythropoietin supports chronic repletion where appropriate. *Coagulopathies* in uremic patients result primarily from platelet dysfunction but also from anemia, coagulation factor abnormalities (e.g., von Willebrand factor), and thrombocytopenia, as well as other coagulopathies due to comorbid conditions, including cancer. Coagulation is usually measured as bleeding time (normally 6–9 minutes); risk of hemorrhage occurs, especially when the bleeding time exceeds 10 minutes. Temporary or partial correction of coagulopathy in preparation for invasive procedures like renal biopsy can be effected by several means, including infusion of cryoprecipitate, synthetic vasopressin, and infused or oral estrogens (70).

Gastrointestinal bleeding occurs in up to one-third of patients with RF, usually due to stress ulcers. It is most often mild but can be life threatening (11,54). Its role in mortality has decreased with improved prophylaxis and therapy with proton pump inhibitors, H_2 blockers, sucralfate, and antacids. One complication of antacid use is that a more alkaline gastric mucosa favors bacterial growth. Sucralfate suppresses gastric acidity less than the other agents and in one study of ventilated ICU patients was associated with fewer latedeveloping pneumonias than ranitidine or antacid (71).

Uremic encephalopathy, as with many clinical consequences of uremia, shows great variations among patients but is generally worse when azotemia develops rapidly. Anorexia, insomnia, and restlessness characterize the first phase, along with decreased attention and mentation. In untreated encephalopathy, emotional lability, decreased ability to think, vomiting, and lethargy follow. The most severe consequences are agitated confusion, dysarthria, and bizarre behavior, proceeding to stupor, coma, and death (72). Convulsions appear in this phase; in two early studies, the incidence of seizures varied from 5–38% (73,74A). The differential diagnosis of such neurological changes includes paraneoplastic encephalopathies, other metabolic disorders (e.g., liver dysfunction), and medication-induced changes in neurological function (e.g., confusion associated with opiates, benzodiazepines, or NSAIDs). Meperidine hydrochloride metabolites, penicillins, and theophylline have all been

associated with seizures. Quiet surroundings, reassurance, and reorientation by a small number of familiar caregivers help patients in the early stages of uremic encephalopathy. However, medication is often needed; for example, benzodiazepines not only calm the patient but also decrease the likelihood of seizures. A useful review of treating delirium at the end of life has been published, but its recommendation of haloperidol is not advisable in patients in RF (74B). Use of the antipsychotics haloperidol and chlorpromazine for confusion are contraindicated due to their lowering the seizure threshold. Many psychotropic medications (see the section Adjustment of Medication) can be given relatively safely to patients with RF; however, dosing regimens must be monitored and individualized to effect (66,75). Advancing neurological symptoms argue strongly for initiation of dialysis in appropriate patients.

Many drugs and their administration, including antineoplastic medications (76,77), are seriously affected by RF and its therapies. Manuals and reviews exist to guide dose and schedule modification in patients in RF, treated with or without various forms of hemofiltration or dialysis (66,78). Use of analgesics, anticonvulsants, and psychotropics in patients dying of RF is discussed in the section Adjustment of Medication.

In developing ARF, the Cockcroft-Gault equation does not allow adequate estimation of creatinine clearance because serum creatinine levels lag behind renal function; recommended dosage guidelines assume creatinine clearance <10 ml/h in patients with declining renal function. During the recovery phase, underdosing may occur as a result of offset between serum creatinine and renal function in the opposite direction. An additional pitfall in recovery is that rising urine flow rates may incorrectly be assumed to correspond with increasing creatinine clearance, which should continue to be measured (79).

Dialysis

In patients with RF not controlled by conservative measures, dialysis is used to correct signs and symptoms of uremia and of electrolyte and acid-base imbalances; to remove fluid overload; to “make room” for other therapies such as nutrition, blood products, and intravenous medications; and to protect the patient prophylactically from complications before their emergent presentation. ARF develops over a few days or less, and in its initial phase azotemia, abnormal electrolytes, and acid-base values may underestimate renal dysfunction. ARF represents a greater threat to homeostasis than does CRF, as there is a longer period for physiological adaptation in the latter. In the presence of significant comorbidities, as often found in cancer patients, a strong case is made for early initiation of dialysis (50,60,80). Dialysis rates for ARF vary according to clinical setting, usually 13–18% for community-acquired or non-ICU patients and 71% in patients in the ICU (8,9). Rates of dialysis for cancer patients (multiple myeloma, RCC, BMT, hematological malignancies) are reported from 9% to 42% (28,29,30 and 31,56).

Although criteria for urgent dialysis vary among nephrologists, the following are frequently used (24,29,80,81): (a) progressive hyperkalemia, e.g., [K+] 6.0–6.5 mEq/l with electrocardiographic changes if not responding rapidly to conservative therapy; (b) severe acidosis with bicarbonate <10 mEq/l and pH <7.20; (c) volume overload with oliguria, pulmonary edema, congestive heart failure, or hypertension resistant to nondialytic therapy; and (d) azotemia, generally blood urea nitrogen levels of 80–120 mg/dl and creatinine levels of 8–10 mg/dl. Dialysis is begun at lower levels of the cited variables when patients have threatening uremic signs and symptoms like pericarditis, encephalopathy, hemorrhage, or vomiting. Rapid development of uremia favors these signs and symptoms. In tumor lysis syndrome, hyperuricemia, hyperkalemia, and hyperphosphatemia with symptomatic hypocalcemia require prompt dialysis. Hypercalcemia with renal compromise in multiple myeloma is another cause for immediate dialysis.

Techniques for renal replacement in RF include intermittent hemodialysis (IHD), slow continuous renal replacement therapy (CRRT), and peritoneal dialysis (PD) (82,83). Different techniques may be used sequentially in a patient; for example, IHD or PD maintenance therapy after emergent correction by IHD or CRRT.

IHD is an efficient means of altering composition and volume of ECF. In patients with life-threatening volume overload or changes in ECF composition, it is often the method of choice. Associated with rapid shifts in electrolytes, this technique can promote cardiac arrhythmias or hypotension, which in turn may cause further renal injury, as can the use of bioincompatible membranes. IHD is poorly tolerated in patients with cardiovascular instability or multiorgan system failure found in 25–50% of hemodialysis patients (82,83 and 84).

CRRT offers the advantages of hemodynamic stability coupled with control of ECF volume and composition in cancer patients with multiple problems, including cardiovascular instability, hypercatabolism, and the need for large volumes of fluids (e.g., medication and nutrition) (80). However, these therapies require indwelling intravascular catheters, patient immobility, intensive nursing care, and careful control of coagulation for days at a time. The indications for IHD and CRRT in ARF continue to be debated (83,84).

PD produces more gradual changes in volume and composition of ECF than IHD does, is less expensive, and requires no anticoagulation. Its use in emergent ARF is increasingly limited, although it is used more frequently in pediatric cases (83). It is widely used in the treatment of CRF. Recent abdominal surgery or the presence of adhesions argue against use of PD, as do abdominal vascular grafts, which can become infected during bouts of peritonitis.

Outcomes of Dialysis

Most patients with ARF (of all causes) either respond to dialysis or die within a month or two of its initiation (11,23,28,29,48). Among cancer patients undergoing dialysis, survival is poor. Mortality among 588 cancer patients dialysed from 1956 through 1993 averaged 62% (2,3 and 4,28,29,30 and 31,56,81,85,86 and 87). Most survivors of ARF of all causes live without dialysis, although some have persistent renal insufficiency (9,10,47,48), and a few (1–3%) require dialysis for ESRD (11,48).

Dialysis is reported for none to nearly one-third of cancer patients with CRF studied (6,31,42,43,47,85). Among 234,296 patients starting dialysis for ESRD from 1989 through 1992, 1.3% had malignant causes for RF. Nearly one-third of these patients died within the first year of treatment, a rate surpassed at that time only by acquired immunodeficiency syndrome patients with ESRD (88). In another study, 10% of 1766 patients starting dialysis for ESRD had cancer and were more likely to withdraw from dialysis than those without cancer (89). In one study of early death on dialysis (113/822 ESRD patients died in 6 months or less), the odds of death were 5–10 times higher for patient with metastatic malignancy and refractory myeloma than all other univariate predictors (90).

The malignancy in which renal disease has been most closely studied is multiple myeloma, in which ARF and CRF are commonly encountered early. Approximately onehalf of these patients respond to dialysis with reversal of RF, usually within 1–2 months. Recovery of renal function and survival are associated with lower serum creatinine on presentation, although in multivariate analysis, myeloma stage and response to therapy were more significant predictors of survival or remission of myeloma than was renal function (23,28,56). Among 1309 patients referred for dialysis with ESRD due to malignancy, median survival for those with multiple myeloma was approximately 1 year, and for those with RCC or amyloidosis, 15–20 months (91).

Making Decisions About Dialysis

What response can we have when faced with population data on one hand and an individual cancer patient with RF on the other? There is no consensus. For at least one author, a diagnosis of cancer should not automatically exclude dialysis (92), and for some, no diagnosis should rule out a trial of dialysis (93). Others cite concerns for cost, limited resources, and individual clinical circumstances in hesitating to initiate dialysis (6,86,94,95). The possibility of withholding and withdrawing life-sustaining therapies subjects patients, families, and caregivers to great stress and difficult ethical dilemmas. Moss (96) and Brody et al. (97), among others, have discussed these problems with specific reference to RF. Recommendations for working through decisions on starting or withdrawing dialysis in both ARF and ESRD have also been addressed in a document written for the Renal Physicians Association and the American Society of Nephrology and supported by related professional organizations (98).

Withholding or Refusing Dialysis

Many authors emphasize physiological limitations and would not begin dialysis for patients with preexistent poor quality of life or short life expectancy (e.g., those with nonuremic dementia or other irreversible neurological disease; patients with end-stage liver, cardiovascular, or lung disease limiting the activities of daily living; and patients with multisystem failure). Some would specifically not use dialysis for patients with metastatic or nonresectable solid tumor or hematological tumors refractory to treatment (94,99,100 and 101), especially with an expected survival of less than 2 years (102).

Some authors do not feel that diagnosis of neoplasm rules out dialysis, especially early in disease (87,92). In myeloma, RF is often found at diagnosis or soon thereafter, before response to antineoplastic therapy is known, and many would agree that dialysis in most of these patients is reasonable (57,87). Sobel et al. state that palliative intervention (including dialysis) for symptoms associated with uremia is appropriate under any of the following circumstances: (a) the clinician feels symptoms will be controlled or performance status will improve with therapy; (b) the patient strongly wishes the therapy despite recommendation against it; and (c) the patient has a prognosis of >2 months and a Karnofsky score of ³50% (95). In many cases of RF, it seems reasonable to give a trial of dialysis for 1–2 months, sometimes longer, and then reconsider its continuation.

In a cancer patient with RF, concerned physicians must balance factors for and against dialysis, including: (a) desires of patient and family concerning treatment; (b) the patient's “baseline” state before RF and likelihood of tolerating and benefiting from dialysis; and (c) the probable course of underlying malignancy and its response to therapy. This task is difficult. A patient's choice is not fixed or immune to education and experience. Estimation of a patient's baseline state involves not only

evaluation of tumor, its stage, and its predicted response to planned therapy, but also a patient's comorbidities, performance status, and psychosocial issues, all of which are difficult to quantify or predict. The Karnofsky and Eastern Cooperative Oncology Group indices are used for prognostic purposes in cancer patients. In one study, the best prognostic model of survival and recovery of renal function used the Acute Physiological Assessment and Chronic Health Evaluation (APACHE II) score (103). In a second study, APACHE III and the Liano models were the best indicators of those patients in ARF who would die regardless of dialysis (8,104).

Finally, physicians should be clear about their own experience and be able to articulate their reasons and feelings about withholding (or discontinuing) dialysis. A wide variety of opinion and practice exists.

In a state-wide survey of ESRD patients, nephrologists withheld dialysis from ESRD patients less often (7%) than did primary care physicians (22%); nephrologists with some training in law and ethics were more likely (12%) to withhold this procedure than those without (6%). In this survey, the presence of cancer was cited by nearly one-half the primary care physicians as a potential reason for withholding dialysis (101). In turning down 25% of 73 dialysis candidates with ESRD due to nonmalignant disease for poor quality of life or a prognosis limited by comorbidity, the physicians encountered no requests for second opinions from patients, families, or referring physicians, and no legal actions occurred (94). Acquiescence by patient and family to treatment denial in more acute settings is likely to be less uniform (96). Estimates are lacking for the number of cancer patients and families who refused dialysis and for what reasons, although it seems safe to assume that variation among deciding factors is probably as wide as that seen among clinicians.

If a decision to begin dialysis for RF in a cancer patient is made, clearly stated clinical goals, including a timetable for reconsidering dialysis, should be accepted by patient and family. If the situation permits—and it often does not— patient and family may need time to consider options and to ask for further guidance from the physician and other caregivers. In any event, timely decisions must be made. Absence of consensus among patient and family and caregivers presents great problems. Empathy, along with identification of and appropriate responses to crucial differences in styles and content (and, in some cases, legal constraints), may help resolve these difficult problems (96,98,102).

Discontinuation of Dialysis

In general, chronic disease (e.g., dementia, cancer) and advanced age are more likely to lead to withdrawal from dialysis (101,105); the same factors are associated with early death in ESRD patients starting dialysis (90,106). Withdrawal of ESRD patients (all etiologies) from dialysis account for 8–53% of deaths in this population (89,100,106,107).

In three studies of ESRD patients of all etiologies, 30–60% of patients were competent, and 50–60% had advance directives (89,101,106). Clinical deterioration accounted for the majority of decisions, although in the largest study, 26 of 66 (39%) competent patients chose to withdraw from dialysis in the absence of obvious medical complications (89). Over the last decades, the discussion of dialysis withdrawal has increasingly been introduced by patients and families rather than by physicians. This may also account for the fact that among 155 patients stopping dialysis, only one case went to court, and none was reported to the bioethics committee (89).

Many oncologists and nephrologists refer those cancer patients refusing or withdrawing from dialysis to hospice. In recent years, the number and percentages of hospice patients dying of nonmalignant disease have increased; in this group, one can include cancer patients dying “early” of RF. The National Hospice Organization (now the National Hospice and Palliative Care Organization) has drawn up guidelines for hospice admission for patients dying of nonmalignant disease. For renal disease, the criteria include (a) creatinine clearance <10 ml/min or serum creatinine >8 mg/dl; (b) ESRD in patients discontinuing or refusing dialysis, and “therefore with uremia, oliguria, intractable hyperkalemia, uremic pericarditis, hepatorenal syndrome, or intractable fluid overload”; and (c) poor prognosis indicated by “mechanical ventilation, malignancy of other organ systems, chronic lung disease, advanced cardiac disease, advanced liver disease, sepsis, immunosuppression/acquired immunodeficiency syndrome, albumin <35 mg/l, cachexia, platelet count <25 × 10^9; age >75 years, disseminated intravascular coagulation, gastrointestinal bleeding” (108). The emphasis on comorbidity is important because most patients dying of RF have more than one important disease process contributing to their demise, very often cardiovascular disease and/or cancer (5,8,9,47,106).

CARE OF CANCER PATIENTS DYING OF RENAL FAILURE

For cancer patients dying of RF, the decision to forgo further curative treatment shifts the focus from “cure and care” to “care only” for alleviation of suffering and for a death as dignified as possible. Support through the terminal phase often entails realignment of responsibilities among the different caregivers in nursing, medical, social work, pastoral fields, and volunteers (1); in hospice, this collection of caregivers is called the *interdisciplinary team*. Nurses and members of the allied services often play a more dominant role in providing hospice care. Physicians should continue to participate in planning and delivery of care; doctors who disappear at this time can create or intensify a sense of abandonment and despair in patients and families as well as in their fellow caregivers. Support and education continue to be given directly to patients, families and friends, and more directly address concerns about dying, death, and grief.

Major signs and symptoms reported in a careful study of the final day of life in patients stopping dialysis were pain, agitation, myoclonus or twitching, dyspnea or agonal breathing, and fever, present in 20–40%; diarrhea, dysphagia, and nausea occurred less frequently (106). Additional symptoms encountered, with emphasis on patients in CRF, included thirst, hiccough, restless legs, itching, Kussmaul breathing associated with metabolic acidosis, and a bad taste in the mouth (109). Treatments of these problems, which are commonly found in dying cancer patients (110,111), are elucidated in other chapters in this book outside the context of RF. Volume overload is of particular concern to RF patients; most ending dialysis are dialyzed to dry weight to protect them from pulmonary congestion in their final days. Thirst is uncommon, and overload is not usually a threat if caregivers do not confuse a dry mouth with thirst and give fluids rather than mouth care. However, if pulmonary congestion does occur, oxygen, opiates, and vasodilators can often control the problem. In a few cases, it may be expedient and appropriate to use existing access for ultrafiltration.

The remainder of this chapter concerns two issues: (a) the adjustment of analgesic, anticonvulsant, and psychotropic medications, which play major roles in symptom control at the end of life, and (b) discussion of a “good” renal death.

Adjustment of Medication

1. Therapeutic preferences and related issues are best discussed with competent patients before discontinuation of dialysis. However, studies show that only approximately one-third to two-thirds of patients withdrawing from dialysis were competent to make their own decisions; 50–60% had advance directives (89,101,106). Even among dialysis patients with advance directives, withdrawal from dialysis is the least discussed option in advance care planning (112). Patients should be encouraged to consider advance directives long before arriving at this point (58,59; see Chapter 63).
2. Significant inter-individual variations in pharmacological parameters and subjective response occur for many drugs in patients with normal renal function. In patients with ESRD, the situation is further complicated by changes in fluid compartment size, reduction or loss of renal metabolism, effects of uremic toxins on other physiological systems, changes in plasma binding, and other comorbidities, including liver function (66). Medication regimens must be tailored to each patient's responses.
3. Medication regimens should be kept as simple as possible. Dosage adjustments for patients usually become less important at the very end of life. Medications with wide therapeutic ranges are helpful because most terminally ill patients do not want to have blood drawn to check drug levels. For example, phenobarbital is preferable to phenytoin as an anticonvulsant as long as the side effects of greater sedation are acceptable to the patient and family.
4. Other interventions should be as noninvasive as possible to avoid disturbing patients. Nonoral delivery is possible with a wide range of medications relevant to end-of-life care, including opiates, NSAIDs, phenothiazines, benzodiazepines, anticonvulsants, antihistamines, antiemetics, scopolamine, dexamethasone, and proton pump inhibitors (113). Increased use of transdermal, rectal, buccal, and other routes minimizes injections to patients no longer able to take oral medication (110,113). Subcutaneous delivery of medication through a percutaneous button or pump obviates repeated injections and is less painful than intramuscular injections, as well as less likely to produce painful intramuscular hematomas, but it is less effective in patients with anasarca. In patients electing not to continue dialysis, retention of central access, if possible, may be helpful by maintaining an intravenous route for medication.
5. Sedation is considered desirable by and for most patients at the end of their lives but not all; one must ask to know.

Pain is common in patients dying in RF (106). Analgesia is needed for most cancer patients, including those in RF, at some time in their illnesses. In CRF, bone changes are a potential source of pain as well. One study shows that analgesia is not achieved in an important fraction of seriously ill patients, even when additional help is available to physicians (114).

Morphine sulfate is the most frequently used strong opiate, although in many situations other strong opiates may be as effective and offer other advantages. Morphine sulfate is glucuronidated in the liver; of the two resultant glucuronides, morphine-6-glucuronide is analgesic. In animal studies, morphine-3-glucuronide is associated not with analgesia, but with hyperactivity and central excitation. Both glucuronides show high dependence on renal excretion for clearance (115). The question arises whether accumulation of morphine-6-glucuronide and morphine-3-glucuronide place patients in RF at increased risk for significant adverse effects of opiates (e.g., respiratory depression, cognitive deficits, obtundation or hyperexcitability, confusion, myoclonus, nausea), many of which may be present in patients in RF who are not taking opiates. Case reports and small series suggest that the answer is yes (26,27,116,117 and 118). Cancer patients (N = 109) with serum creatinine ranging 0.5–8.0 mg/dl did not show significant association of myoclonus (especially common in patients with RF) or decreased cognitive function with increased

morphine-6-glucuronide/morphine sulfate ratios; however, very high plasma levels of morphine-6-glucuronide in the presence of other metabolic abnormalities (e.g., liver dysfunction as indicated by elevated LDH and bilirubin) were associated with respiratory depression or obtundation in a small number of patients (26). In another study, 19 of 36 cancer patients in hospice were found to have increased nausea and vomiting (N = 10) and delirium (N = 9). As a group, the symptomatic patients had a mean serum creatinine twice that of the 17 patients without these symptoms; however, many of the symptomatic patients had serum creatinine in normal range (27). More studies are needed to refine the relationship of opiates and unwanted side effects in patients with RF.

Information on the effects of metabolite accumulation for other opiates in RF is scanty. Metabolites of hydromorphone (Dilaudid) accumulate in patients with RF. Hydromorphone-3-glucuronide appears to be associated with hyperalgesia, excitatory behavior, and respiratory stimulation (118). Normeperidine, a metabolite of meperidine hydrochloride (Demerol), accumulates in RF and facilitates seizures; for this reason, meperidine hydrochloride should not be used in patients with RF. Both fentanyl (66) and oxycodone hydrochloride (119,120) accumulate in patients with RF. Among weaker opiates, codeine phosphate metabolites show some accumulation in patients in RF and need dose adjustment (66).

Analgesia must be provided to patients in pain as long as they desire it. It is suggested that patients with creatinine clearances of 10–50 ml/min receive a 25% reduction in doses of morphine sulfate or codeine phosphate and that those with creatinine clearances <10 ml/min receive 50% eduction in morphine sulfate and codeine phosphate doses 66). These dose reductions are initial estimates; each patient must be titrated individually for optimal combination of effective analgesia and tolerable side effects. Trials of alternative opiates with adjustment for partial cross tolerance can be helpful.

Analgesia for neuropathic pain may include tricyclic antidepressants, anticonvulsants, and other agents (e.g., clonidine). Nortriptyline hydrochloride and desipramine hydrochloride, tricyclic antidepressants with fewer anticholinergic side effects and a wider therapeutic window than amitriptyline hydrochloride, are used for dull, burning dysesthesias. They can be continued without dose adjustment as long as the patient can take oral medication; parenteral amitriptyline hydrochloride is now available for continued neuropathic coverage. Carbamazepine and phenytoin, anticonvulsants used for lancinating neuropathic pain, can be given without dose adjustment. Gabapentin, an anticonvulsant widely used for burning dysesthesias and lancinating pains, needs dose reduction in patients with RF; for those with creatinine clearances <10 ml/min, 300 mg every other day is sufficient as long as the patient can take medication orally (66).

Some cancer patients with intractable pain, especially neuropathic pain, have received relief from oral, transdermal, or epidural clonidine (121). The medication undergoes significant renal metabolism, can cause sedation and hypotension, and interacts with other medications often used for cancer patients (e.g., tricyclic antidepressants, barbiturates, and other sedatives). However, in transdermal form, it also has been effective in a subpopulation of patients with diabetic neuropathy (122). This route makes it attractive for use in dying patients, although studies of its use in patients dying of ESRD are lacking. In patients with neuropathic pain poorly controlled with other medications, cautious use may be undertaken if patient and family accept the risk.

In addition to opiates and NSAIDs, bisphosphonates (e.g., pamidronate disodium) may be helpful in combating pain due to bony metastases and can be administered by either intravenous or oral routes (123). Data on this use in ESRD patients are lacking, but intravenous bisphosphonates require small fluid loads (250–500 ml) and, of little importance here, may worsen azotemia. Despite their nephrotoxicity, NSAIDs for bony pain may become more relevant in the terminal phase. However, these patients are at greater risk for uremic gastritis and hemorrhage, even with protection of the gastric mucosa. The same risk occurs with the oral or subcutaneous use of corticosteroids for bony pain, although in some orchidectomized patients with prostate carcinoma, small doses (1–2 mg twice a day) of dexamethasone may offer good analgesia with few, if any, risks or side effects. The combination of NSAIDs and corticosteroids should be avoided if possible. For gastroprotection, H_2 blockade is given orally or intravenously in reduced doses for patients with RF, whereas proton pump inhibitors and misoprostol can be given only orally but need no dose adjustment (66).

Phenytoin and phenobarbital are the primary anticonvulsants in terminal patients with ESRD (124). Phenobarbital has a wide therapeutic range and can be given by several routes: oral, subcutaneous, intravenous, or intramuscular. In ESRD, it should be started at 75% of its usual range and adjusted. Less sedating than phenobarbital, phenytoin can be given either orally or intravenously. In ESRD, it has a lower and narrower therapeutic range than in patients with normal renal function, as a result of decreased protein binding. In patients allergic to phenobarbital and phenytoin, carbamazepine is an alternative choice for tonic-clonic seizures as well as for the less frequent partial and complex partial seizures. However, like gabapentin, it can only be given orally.

Benzodiazepines are used to relieve anxiety and to treat myoclonus arising either from accumulation of opiates or intrinsic to uremia, as well as to treat seizures. In general, benzodiazepines with shorter half-lives and no clinically active metabolites (e.g., lorazepam, clonazepam, oxazepam, and temazepam) are preferred to diazepam, with its longer half-life, unless sedation or seizure control are specifically sought. Benzodiazepines can be given initially without dose adjustment and then titrated to effect. Like barbiturates, they may cause respiratory depression.

Midazolam hydrochloride, a benzodiazepine with a short half-life, administered intravenously, subcutaneously, or intramuscularly, is helpful in patients with myoclonus, anxiety, terminal agitation, and, in some cases, seizures (125). In severe RF and in the elderly, 50% of the normal dose is used (66). For patients with multifocal myoclonus, an initial dose of 2–5 mg subcutaneously every hour is recommended until myoclonus is controlled, followed by continuous pump-delivered subcutaneous or intravenous doses. The same approach and initial dose may be used for moribund patients with grand mal seizures (110). Increased infusion rates are often necessary because of midazolam hydrochloride's marked tachyphylaxis.

Agitated confusion is common in cancer patients dying of RF. Sedation is often preferable to patient and family. Benzodiazepines and barbiturates become drugs of choice over antipsychotic medication, especially in the last days of life. In this situation, diazepam may be preferred over shorter-acting benzodiazepines; midazolam hydrochloride is also useful, although tachyphylaxis can complicate its titration. Pentobarbital or phenobarbital can produce a welcome deep sedation. In patients with i.v. access, midazolam hydrochloride 2.5 mg infused over 2 minutes can produce emergency sedation during a catastrophic terminal event.

Among drugs to treat confusion, haloperidol, chlorpromazine, and other high-potency antipsychotics have a greater propensity to promote seizures. These medications undergo extensive hepatic metabolism. Haloperidol is used without dose adjustment to treat nausea and vomiting and is probably safe if used infrequently in low doses. Confusion at this stage of life is more effectively treated with sedating medications like benzodiazepines or barbiturates.

A Good Death in Renal Failure

Many caregivers have clear ideas and strong feelings about what characterizes an acceptable or peaceful death for their patients, and many have focused on these issues in books and articles in the hospice literature. One study (126) reports the attributes of a good death as defined by discussion in focus groups and in-depth interviews with patients, surviving family members, and caregivers (nurses, social workers, chaplain, hospice volunteers, and physicians). Despite the small numbers in each category (total N = 75), the results seem appropriate and probably approximate the thoughts and feelings of many. The six components of a good death were as follows: (a) good pain and symptom management; (b) clear decision-making shared by patients/families and caregivers; (c) preparation for death in both physical and psychosocial dimensions; (d) completion through life reviews, connectedness to others, and resolution of conflicts; (e) contributing to others' well-being; and (f) affirmation of the patient as a whole person, perceived and treated as unique and valuable. The authors point out each attribute “has a biomedical, psychological, social and spiritual component.” Professional roles were evident in discussion. As a group, physicians (N = 6) were more exclusively medical; none spoke of contributing to others as an aspect of a good death and only one mentioned completion. The other caregiver groups recognized all six attributes.

In contrast, explicit definition of criteria of a good death and their application in actual patients dying of RF is rarely published. After a preliminary report (127), an interdisciplinary team reported a mixed retrospective-prospective study of the course of ESRD patients after discontinuation of dialysis. Three-quarters of the fully studied 79 patients had three to seven comorbidities, and 12% had malignancies. Median time to death after dialysis discontinuation was 6 days in 126 patients; the average was 8 days. Some patients lived for 30–46 days, and ten debilitated patients lived less than 2 days (106).

In their original report (127), the authors measured quality of death by quantitating three components: (a) duration of dying after stopping dialysis; (b) presence of physical suffering; and (c) consideration of psychosocial issues (e.g., decision-making process, level of awareness, involvement of family and friends). The category of “good death” included 7 of 11 prospectively studied patients. The remaining four patients' courses after discontinuation of dialysis were compromised by “varying degrees of pain, confusion, agitation, social unrest, and a longer than average survival.” Cohen and his collaborators have published an instrument measuring quality of life in patients with ESRD. It combines relevant physical and psychosocial parameters, the peace and dignity of each death, and the duration of life between stopping dialysis and death in a quantitative index of a “good death” (128).

In the later study (106), caregivers or families felt that treatment was effective in the last 24 hours of life for 93% of patients, a marked improvement over the figures found in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (114). Nonetheless, among 79 prospectively followed patients during this time, pain occurred in 42% (severe in 5%), agitation in 30% (severe in 1%), myoclonus in 28% (severe in 4%), and dyspnea/agonal breathing in 25 (severe in 3%). Pain medication was used at least once after stopping dialysis in 87% of patients. Although none needed ultrafiltration for pulmonary edema, 22% used oxygen. The authors in discussion ask if treatment can be considered acceptable or effective in the presence of these numbers (106). The incidence of pain and dyspnea among patients dying of ESRD is not greatly different from a similar list of disturbances found in 400 hospice patients in the last day of life, although myoclonus is greater among those with ESRD (111).

SUMMARY

RF is a common occurrence in cancer patients. It may be present at diagnosis or arise during therapy and bring about the patient's death. In the specialized world of contemporary medicine, the oncologist's most important functions with regard to RF are prevention, referral, and collaboration—prevention in designing and providing therapy, referral to a nephrologist when renal function is deteriorating, and collaboration with patient, family, and other clinicians throughout the patient's course. Collaboration is often difficult because of the different expertise, experience, and expectations of those involved. Knowledge, patience, practice, and a steady focus on the patient's and family's needs and desires are all-important to effective care.

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34

HYPERCALCEMIA

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Hypercalcemia may occur in as many as 8–10% of patients with malignancy during the course of their disease, making it one of the most common metabolic complications of cancer. Despite this high frequency, the diagnosis of hypercalcemia is often delayed. An awareness of the tumor types most commonly associated with hypercalcemia, the mechanisms giving rise to hypercalcemia, and the symptoms produced permits earlier diagnosis and amelioration of morbidity by the use of effective therapeutic interventions.

Since it was first reported in 1924 (1), hypercalcemia has become well recognized in association with various malignant diseases. The mechanisms responsible for the production of hypercalcemia have been increasingly well defined. Hypercalcemia is most commonly seen in association with squamous cell carcinoma of the lung, carcinoma of the breast, and multiple myeloma. This distribution of tumor types associated with hypercalcemia has remained relatively constant (2,3). Some tumors, including small cell carcinoma of the lung and carcinoma of the prostate (which frequently metastasize to bone), as well as other common tumors such as adenocarcinoma of the colon and stomach, are rarely associated with hypercalcemia, despite biochemical and histomorphometric data indicating enhanced bone resorption (notably in the case of carcinoma of the prostate) (4). The relative frequency of other tumor types associated with hypercalcemia seems to vary with the area of special interest of the investigators reporting the complication. Nevertheless, hypercalcemia is well recognized with squamous tumors of the head and neck and genitourinary neoplasms.

Patients with hypercalcemia and malignant disease are usually in the last weeks of their lives unless effective antitumor therapy is available. Therefore, therapeutic interventions must be as innocuous as they are effective. With modern therapeutic agents, it is possible to restore normocalcemia in most patients without inducing serious side effects.

ETIOLOGY OF HYPERCALCEMIA IN MALIGNANT DISEASE

A brief review of normal bone and calcium metabolism is important in enhancing the understanding of the mechanisms that lead to hypercalcemia and provides a framework for intelligent therapeutic intervention.

Bone is a dynamic structure that undergoes constant remodeling. The remodeling process is a highly integrated interaction between several cell types (5), the two most important of which are the osteoblasts, or bone-forming cells, and the osteoclasts, or bone-resorbing cells. Responding to as yet incompletely understood stimuli, osteoclasts resorb an area of bone that is to be remodeled over a period of approximately 10 days. Osteoclastic resorption involves the enzymatic degradation of bone proteins such as collagen and the release of calcium from the mineral phase of the bone. The resorption phase is followed by a reversal phase, during which the osteoclasts disappear to be replaced by mononuclear cells. Thereafter, a bone-formation phase, lasting several months, occurs in which osteoblasts lay down new bone to repair the defect. To maintain the strength and integrity of the bone, the resorption and formation phases are closely coupled. It is easy to see that any process that could increase osteoclastic bone resorption or decrease osteoblastic bone formation would lead to an increased net calcium flux into the extracellular fluid, which would have to be excreted by the kidneys. If the degree of imbalance is small, a disease process such as osteoporosis would result; however, if the degree of imbalance is quite large, widespread bone lysis and hypercalcemia could be expected.

The adult human body contains approximately 1 kg of calcium, of which all but 10 g is lodged in bone. Minute intracellular concentrations of calcium (10^{-8} to 10^{-7} molar) are vital to normal cellular function, but most of the nonosseous calcium is present in the extracellular fluid. Under normal circumstances, total body calcium represents a steady state between calcium intake and excretion. Somewhere between 25% and 50% of the dietary calcium intake of approximately 1.0–1.5 g per day is absorbed. Although bone represents an enormous reservoir of calcium, little transfer (approximately 500 mg, or 12.5 mmol, per day) occurs between bone and the plasma in the state of good health (6). When net calcium balance is zero, the kidneys are required to excrete approximately 150 mg of calcium daily. Glomerular filtration of non-protein bound calcium is approximately 10 g/day, 65% of which is reabsorbed in the proximal convoluted tubule and 25% in the ascending limb of the loop of Henle, in which resorption is independent of hormonal control. Proximal nephron calcium reabsorption is closely linked to sodium reabsorption. In situations of volume depletion (such as those induced by hypercalcemia), inappropriate calcium retention may occur as the kidney attempts to conserve sodium and hence extracellular fluid volume. A variable amount of the remaining calcium is reabsorbed from the distal convoluted tubule. Calcium reabsorption in this area is increased in the presence of parathyroid hormone (PTH), and it is at this site that the fine-tuning of calcium homeostasis occurs. Renal calcium losses can increase to accommodate an increase in bone turnover of approximately 150% before hypercalcemia occurs.

The routinely measured total plasma calcium concentration is composed of a combination of physiologically active or ionized calcium, accounting for approximately 45% of the total, protein-bound calcium (the bulk of which is bound to albumin and accounts for approximately 45% of the total), and the remainder (10%), which is complexed with ions such as bicarbonate and citrate. In terms of patient management, the ionized calcium concentration carries the greatest significance. Although ion-specific electrode measurement of ionized calcium is available, most centers routinely measure the total serum calcium. The correlation between total serum calcium and ionized calcium is, at best, only fair. The proportion of the total calcium in the unbound or physiologically active state varies with, among other things, the albumin concentration. Numerous algorithms have been designed to attempt to “correct” total serum calcium, particularly in the face of reduced albumin concentrations. The algorithms listed here are clinically useful, and it is imperative that clinical decisions are made not on the basis of a total calcium but at the very least a corrected calcium (7,8).

Ca (corrected) = Ca (measured) + [0.8 × (4–albumin concentration)] *Conventional Units*

Ca (corrected) = Ca (measured) + [0.02 × (40–albumin concentration)] *SI Units*

Under normal circumstances, calcium and bone metabolism are tightly regulated by the action of three main hormones.

PTH is an 84 amino acid polypeptide secreted by the parathyroid glands in response to low ionized serum calcium. It enhances calcium resorption from bone by an indirect action on osteoclasts. In addition, PTH diminishes distal nephron calcium excretion and, by its action on the renal 1-a hydroxylase, increases circulating $1,25\text{-}(OH)_2D_3$ (di-hydroxyvitamin D_3, the main active metabolite of the vitamin D complex of sterols).

Most of the biological activity of PTH is contained within the first 34 amino acid residues (9). This is of clinical significance because this amino acid sequence is shared in part with a tumor product, PTH-related peptide (PTHrP), discussed in the section Parathyroid Hormone-Related Protein.

The vitamin D complex is a group of steroid hormones with important effects on bone metabolism and calcium homeostasis. The main active metabolite is $1,25\text{-}(OH)_2D_3$. Hydroxylation of vitamin D is a two-step process. The 25-hydroxylation takes place in the liver and is substrate dependent. Conversion to the active dihydroxy metabolite is the rate-limiting step, which takes place in the kidney and is stimulated by PTH (vide supra) and inhibited by $1,25\text{-}(OH)_2D_3$. Vitamin D brings about its effects by increasing calcium absorption from the gastrointestinal tract and enhancing calcium reabsorption in the kidney.

Calcitonin, the physiological antagonist to PTH, is a 32 amino acid polypeptide hormone secreted by the C cells of the thyroid gland. Using time-lapse photography, calcitonin can be seen to have a powerful and rapid suppressive action on osteoclast activity. Down-regulation of calcitonin receptors is known to occur, making its clinical effects generally short lived. The true physiological role for calcitonin is unclear because biochemical disturbances are unusual in patients who have had complete thyroidectomies and in patients with extremely high levels in medullar carcinoma of the thyroid gland. It may be that calcitonin is a physiological regulator of postprandial hypercalcemia (10).

Two main mechanisms contribute to the development of hypercalcemia in most patients with malignancy. In local osteolytic hypercalcemia, tumor invasion of bone causes release of large amounts of calcium from destroyed areas of bone. In the humoral hypercalcemia of malignancy, the effects of PTH are mimicked by PTHrP. In this situation, renal tubular reabsorption of filtered calcium is increased in addition to the increased generalized osteoclastic activity throughout the skeleton. These mechanisms are not mutually exclusive because many tumor types that metastasize to bone also manufacture PTHrP. Enhanced gastrointestinal absorption of calcium is a rare mechanism for hypercalcemia of malignancy, limited mainly to hematological disorders.

Local Osteolytic Hypercalcemia

Metastatic tumor cells are capable of resorbing bone directly (11), although the classic studies of Galasko (12) suggest that much of the resorption is carried out by osteoclasts. The tumor types commonly associated with this form of hypercalcemia are carcinoma of the breast, multiple myeloma, and other hematological malignancies. A large bony burden of tumor is usually required to produce the hypercalcemia.

Carcinoma of the Breast

Hypercalcemia is an infrequent finding in patients with carcinoma of the breast in the absence of widespread osseous metastases. Histological evidence demonstrates that bone destruction is mediated by osteoclasts in close proximity to tumor cells. Breast cancer cell growth regulation is thought to occur in part under the influence of a number of closely associated growth factors (13). Epidermal growth factor and transforming growth factor alpha (TGF-a) are produced in a paracrine fashion at the site of bone metastases. These substances, which share a common receptor, are potent stimulators of osteoclastic bone resorption. Both TGF-a and epidermal growth factor can be found by immunohistological techniques in breast cancer cells. The local release (particularly of TGF-a) in bone could be predicted both to increase metastasis growth and to enhance osteoclastic activation and bone resorption, thereby making room for the multiplying tumor cells.

In their classic studies, Galasko and Bennett (14) demonstrated that osteoclast recruitment and bone destruction stimulated by implants of the VX_2 carcinoma in rabbits could be reduced by the oral administration of the cyclooxygenase inhibitor indomethacin. Confirmatory evidence for a role for prostaglandins in the development of metastases came from Powles et al. (15), who showed that cyclooxygenase inhibitors reduced the incidence of bone metastases in rats bearing the Walker tumor. Unfortunately, the use of prostaglandin synthesis inhibitors has not been effective in influencing the course of metastatic bone disease in patients with breast cancer.

Despite the fact that most hypercalcemic breast cancer patients have a significant bony metastatic burden, it is clear that not all cases are due to local factors. An enhanced tubular reabsorption of calcium in breast cancer patients has been demonstrated (16). In this study, the authors concluded that approximately 40% of the observed hypercalcemia was accounted for by a renal mechanism. It is known that breast cancer cells can produce and secrete PTHrP; indeed, one of the original tumor types from which PTHrP was isolated was breast cancer (17). In fact, serum elevation and tumor histochemical localization of PTHrP is common in breast cancer patients, even before the development of hypercalcemia (18). Furthermore, there are increasing data that PTHrP may have a role in the development and maintenance of bone metastases in patients with breast cancer (19).

Multiple Myeloma

In patients with multiple myeloma, there is an intimate association between the malignant plasma cells and the bone marrow. Fracturing, osteopenia, and hypercalcemia are frequent complications in these patients. Histological studies have shown a close association between myeloma cells and activated osteoclasts. Over the last 20 years, significant advances have been made in elucidating the mechanisms of the bone resorption in multiple myeloma. In the mid-1970s, Mundy et al. (20) demonstrated that supernatants from myeloma cells in tissue culture had osteoclastactivating activity that lead to the mobilization of ^{45}Ca from fetal rat long bones. These substances were descriptively named *osteoclast-activating factors*. It has become increasingly clear that more than one substance elaborated by multiple myeloma cells has osteoclast-activating factor activity. Several groups of investigators have identified potent osteoclast-activating properties associated with various multifunctional cytokines, including lymphotoxin (TNF-b) (21), interleukin-1 (IL-1) (22), and interleukin-6 (IL-6) (23). Many of these same factors are also potent inhibitors of osteoblastic bone formation. Furthermore, elevated levels of PTHrP have been found in almost onethird of hypercalcemia multiple myeloma patients in a study by Firkin et al. (24).

The multifunctional cytokine IL-6 is well recognized as a growth promoter for myeloma cells. It potentiates the actions of other bone-resorbing cytokines such as IL-1 and lymphotoxin, although its effect on bone metabolism is not clear. Levels of IL-6 increase in the advanced phases of disease when widespread osteopenia is manifest, although a direct cause and effect phenomenon cannot be inferred.

Patients with multiple myeloma frequently have abnormal renal function. Reductions in glomerular filtration rate caused by myeloma kidney or light-chain nephropathy hamper the ability of the body to excrete the excessive calcium load. Furthermore, the calcium elevation itself is also nephrotoxic and can lead to a vicious cycle of deteriorating renal function and hypercalcemia.

In rare patients with multiple myeloma or monoclonal gammopathy of undetermined significance, the phenomenon of pseudohypercalcemia may occur (25). In this situation, calcium becomes bound to nonalbumin plasma proteins, resulting in a spuriously elevated total serum calcium concentration. The ionized calcium concentration is normal under these circumstances, but correction formulae using albumin will give falsely abnormal results.

Humoral Hypercalcemia of Malignancy

The concept of a humoral factor being responsible for the genesis of hypercalcemia is not a new one. In 1941, Fuller Albright (26) described the case of a patient with a renal cell carcinoma who was significantly hypercalcemic despite a very low bony metastatic burden. This patient also had significant hypophosphatemia, and the clinical features suggestive of primary hyperparathyroidism had been enough to lead the surgeons to perform a neck exploration. Although PTH could not be recovered from biopsy material from the tumor, Albright postulated that a humoral factor secreted by the tumor was responsible for the hypercalcemia. Indeed, the term *pseudohyperparathyroidism* was popularized in the 1960s (27,28).

In their extensive metabolic evaluation of 50 patients with hypercalcemia and malignant disease in 1980, Stewart et al. (29) divided the patients into two groups. One group shared the features of primary hyperparathyroidism, including a tendency to hypophosphatemia, a lowered renal phosphate threshold, and an elevated nephrogenous cyclic adenosine monophosphate (NcAMP) excretion. These patients mostly had squamous carcinomas, renal carcinomas, and urothelial malignancies. The second group, who mostly had metastatic carcinoma of the breast and multiple myeloma, had low levels of NcAMP excretion. The authors concluded that urinary NcAMP was a surrogate marker for a circulating substance that had PTH-like activity. Using assays available at the time, they were unable to detect elevated levels of PTH in the sera of these patients.

Although they continue to be rare, anecdotal reports of ectopic PTH production causing hypercalcemia (30) do occur; however, native PTH is not the substance responsible for most cases of humoral hypercalcemia of malignancy. The strongest evidence came from the fact that using complementary DNA techniques, Simpson et al. (31) failed to demonstrate the production of PTH by tumors commonly associated with hypercalcemia. The development of a sensitive two-site immunoradiometric assay for PTH helped considerably to overcome the problems of measuring this compound, which has a very short plasma half-life but many products of metabolism that interfere with more conventional assays (32).

Parathyroid Hormone–Related Protein

In 1987, three groups independently published descriptions of a novel polypeptide hormone that had been isolated from tumors associated with the hypercalcemia of malignancy (17,33,34). PTH-related protein is a much larger molecule than PTH. Although the predominant circulating form of PTHrP is not yet known with certainty, the original authors describe several isoforms of this hormone, including 139, 141, and 173 amino acid residues that arise by alternative splicing of RNA and differ only in their carboxy termini. The primary structure of these peptides shows considerable N-terminal homology with native PTH, with 8 of the first 13 amino acids being identical; PTHrP interacts with the PTH receptor with equal affinity to the native hormone, accounting for its ability to mimic both the renal and bony effects of PTH. Many normal fetal and adult tissues produce PTHrP. The physiological roles of PTHrP are complex and have been the subject of a recent review by Strewler (35). The hormone appears to have a number of different functions at an autocrine and paracrine level depending on its site of production. Furthermore, PTHrP appears to be a polyhormone (i.e., there are receptors for different regions of the molecule). The amino terminal end shares a common receptor with PTH (and is the part of the molecule responsible for hypercalcemia of malignancy). The midregion of the molecule (amino acids 38–94) may be the main stimulus for the placental calcium pump. The carboxy terminal appears to inhibit bone resorption and may also act within the central nervous system. Data are also appearing to suggest that PTHrP may have a role in regulating renal function and repair after acute renal failure (36). PTHrP has been identified immunohistochemically in divergent areas throughout the kidney including the glomeruli, tubules, and arterial tree. Its exact role in these situations remains uncertain.

Definitive evidence for the biological activity of PTHrP having a causal role in hypercalcemia of malignancy came from studies in nude mice bearing a human tumor responsible for hypercalcemia. By causing an antiserum directed against synthetic human PTHrP, Kukreja et al. (37) were able to reverse the biochemical abnormalities of hypercalcemia, hypophosphatemia, and increased NcAMP excretion in these animals. These experiments provided strong evidence that PTHrP was directly responsible for the hypercalcemia.

The development of assays for PTHrP has been plagued by similar problems as those for PTH. The levels in normal serum are quite low (below 2.5 pmol/l), and the nature and reactivity of metabolic byproducts is not clear. Two-site immunoradiometric assays have been developed and are more sensitive. Using a midregional assay, Blind et al. (38) reported that 81% of hypercalcemic patients who had squamous tumors had an elevated PTHrP level. Studies using two-site assays have detected elevated serum levels of PTHrP in 90–95% of patients with squamous carcinomas and hypercalcemia (39,40).

Whereas PTHrP is commonly considered in the context of humoral hypercalcemia, there are interesting reports of its relationship to bone metastases in patients with breast cancer. Powell et al. reported that 92% of bony metastases from breast cancer stain positive for PTHrP immunohistochemically compared with only 17% of metastases at other sites (41).

Vitamin D

Levels of 1,25-$(OH)_2D_3$ are low in most cases of hypercalcemia of malignancy; however, there are a group of malignant (and some nonmalignant) disorders in which 1,25-$(OH)_2D_3$ is elevated and acts as a humoral mediator of hypercalcemia. It has been known for more than 10 years that granulomatous conditions, such as sarcoidosis (42), are associated with extrarenal synthesis of 1,25-$(OH)_2D_3$. The site of the ectopic 1-a hydroxylation is presumably in the macrophages associated with the granulomata. Davies et al. (43) described a substrate-dependent conversion of 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3 in a hypercalcemic patient with Hodgkin's disease exposed to increased levels of sunlight. This response was no longer seen after successful treatment of the malignancy. Although occasional case reports of hypercalcemia and abnormally elevated 1,25-$(OH)_2D_3$ have appeared in the literature (44,45), hypercalcemia remains an uncommon complication of hematological malignancies other than myeloma. In a large series of 217 patients with advanced lymphoma, only four cases of hypercalcemia were reported (46).

A significant exception to the rare finding of hypercalcemia in lymphomas is adult T-cell lymphoma, an uncommon tumor in North America that appears to be associated with infection with the human T-cell lymphotropic virus type 1. More than half of these patients develop hypercalcemia, which is a common cause of death. Although elevated 1,25-$(OH)_2D_3$ levels have been reported in these patients, there is also evidence for elevation in PTHrP levels, suggesting that an interaction of humoral mediators may be responsible (47).

Other Hypercalcemic Factors

Case reports and animal studies have added significantly to the number of mediators that may be responsible for hypercalcemia in malignant disease. Squamous carcinomas have been reported to produce IL-1 either in the presence (48) or absence (49) of hypercalcemia. Furthermore, these tumors also secrete colony-stimulating factors, which may enhance osteoclast precursor generation. Indeed, simultaneous tumor production of IL-1 and PTHrP has been demonstrated (50), and these two hypercalcemic factors may interact synergistically *in vitro* and *in vivo* (51). Cose-cretion of IL-6 and PTHrP also has been described (52). Similarly, tumor production of prostaglandins associated with the development of hypercalcemia is also well recognized (53). Squamous carcinoma cell lines associated with humoral hypercalcemia of malignancy have been shown to secrete an osteoclast differentiation factor (ODF) [also called *tumor necrosis factor-related activation-induced cytokine* (TRANCE)]. This factor is able to induce the differentiation of HL60 promyeloblastic leukemia cells into osteoclasts (54). Formation and secretion of ODF/TRANCE directly by malignant cells may enhance osteoclast number by recruitment and differentiation, in addition to that caused by the effects of PTHrP.

Although PTH is rarely the humoral factor causing hypercalcemia, secreting carcinomas of the parathyroid glands may occur. In the rare group of multiple endocrine neoplasia syndromes, hyperparathyroidism and asymptomatic hypercalcemia due to PTH secretion is common.

EVALUATION OF THE HYPERCALCEMIC PATIENT

Hypercalcemia usually occurs in the face of overt malignancy, and so the diagnosis as to the cause of the hypercalcemia is rarely in doubt. In spite of this fact, it is worth considering other causes of hypercalcemia (Table 34-1), which may be readily amenable to therapeutic intervention. Additionally, aggravating factors such as immobilization should be sought and attempts made to rectify these factors.

Endocrine	Hyperparathyroidism
	Hyperthyroidism
	Addison disease
Iatrogenic	Immobilization
	Vitamins A and D
	Thiazide diuretics
	Lithium carbonate
Other	Paget disease of bone
	Granulomatous disease

TABLE 34-1. NONMALIGNANT CAUSES OF HYPERCALCEMIA

Clinical Findings

The symptoms of hypercalcemia are often vague and nonspecific. Furthermore, there is an imperfect correlation between calcium level and degree of symptomatology. Indeed, severe hypercalcemia may be an incidental finding on a biochemical screen of a patient with malignant disease. The rate of development of hypercalcemia may influence the occurrence of symptoms.

Gastrointestinal upset occurs in most symptomatic individuals. Nausea, anorexia, and vomiting are common, but they may be ascribed to the side effects of chemotherapy or to symptoms produced by the tumor itself. By inducing dehydration and hence aggravating the hypercalcemia, these complications set up a vicious cycle. Constipation is common, and complete ileus may occur at severely raised calcium levels. Cramping abdominal pains such as those seen in primary hyperparathyroidism are encountered occasionally, but acute pancreatitis or peptic ulceration complicating the hypercalcemia of malignancy is extremely rare. It is

likely that the relative acuteness of the disease as compared with, for example, primary hyperparathyroidism, accounts for the low incidence of these latter adverse effects.

Hypercalcemia *per se* is toxic to the renal tubules. It causes a reversible impairment in renal concentrating ability, resulting in the production of large volumes of dilute urine. This polyuria serves to aggravate the volume depletion produced by the gastrointestinal effects and results in a fall in the glomerular filtration rate, which in turn causes further impairment of the kidney's ability to handle the abnormal calcium load, and the vicious cycle continues.

Although the major disturbance in tubular function is related to changes in urinary concentrating ability, another important renal effect is that of an inappropriate natriuresis. The extracellular fluid volume contraction results in attempts by the proximal tubule to conserve sodium, and because of a linkage between renal sodium and calcium handling, calcium is also retained. Despite the fact that the thirst mechanism is intact and polydypsia occurs, the gastrointestinal upset is often so great that severe volume depletion occurs. Impaired mental status may further compromise fluid intake. Solute washout of potassium and magnesium can occur as a result of the polyuria, and some of the neuromuscular effects of hypercalcemia can be aggravated by relative deficiencies of these ions.

Hypercalcemia frequently is overlooked as a cause of neuropsychiatric symptoms in patients with advanced malignant disease. Rather, these are often ascribed to the underlying neoplasm or to medications the patient may be taking, such as narcotic analgesics, antiemetics, or sedatives. Muscle weakness may be profound, confining the patient to bed and aggravating the hypercalcemia because of immobility. As hypercalcemia worsens, confusion and finally coma supervene. Reversible focal neurological symptoms with hypercalcemia have been reported but are rare.

Cardiac muscle appears relatively immune to the effects of hypercalcemia, which has a digitalis-like effect on cardiac contractility. Reduction of the QT_c may be observed occasionally on ECG, but unless the patient is given cardiac glycosides, the cardiac effects are of little clinical significance. Arrhythmias are more likely to occur because of associated hypokalemia or hypomagnesemia during the treatment phase, in which rapid intravascular volume expansion is occurring.

Bone pain is a frequent symptom of both malignant disease and hypercalcemia. Although this pain may be due in part to the presence of bony metastases, the symptom is also present in the absence of demonstrable metastatic disease. Calcium may act as a neurosensitizer, decreasing the pain threshold, but the precise mechanism of pain generation in hypercalcemia is unclear.

The syndrome of hypercalcemia of malignancy, therefore, presents itself with anorexia, fatigue, apathy, and polyuria but may rapidly progress to obtundation and death.

Laboratory Investigations

The diagnosis and management of hypercalcemia in a patient with malignant disease require little in the way of investigations. A complete blood count with estimation of the platelet count should be performed, and measurement of serum electrolytes, blood urea nitrogen, and creatinine is mandatory. The ionized calcium level is the best clinically relevant measurement to perform; however, it is less readily available and more expensive than a total calcium level. The total serum calcium level is a poor indicator of the biologically active component and should not be used alone to direct initial management without the use of a correction algorithm to take into account the effect of altered albumin concentrations. In asymptomatic patients with hypercalcemia and multiple myeloma, a serum ionized calcium should be obtained to exclude pseudohypercalcemia.

Renal function and the response of the calcium to therapy should be monitored daily until the calcium concentration normalizes. Close attention should be paid to changes in potassium and magnesium levels, which may drop dramatically during the early treatment phase because of volume expansion and increased glomerular filtration rate as the hypercalcemia is corrected. An underlying potassium deficiency caused by poor dietary intake is frequently unmasked at this time. Serum phosphate levels may fall precipitously in some patients, particularly when potent antiresorptive therapy is used.

Once the calcium level returns to normal, weekly estimation can act as a guide to the need for further antihypercalcemia therapy. Of course, investigations should be individualized depending on the patient's clinical condition and response to therapy.

From the academic viewpoint, greater insight into the mechanism behind the hypercalcemia can be gained from more complex investigations. These have few practical implications given the current therapeutic options but may become more relevant if, for example, effective blockade of the PTH receptor becomes possible or monoclonal antibodies to PTHrP are developed for clinical use. In the absence of a readily available assay for PTHrP, biochemical clues to its presence include hypophosphatemia, hyperchloremia, and a mild metabolic acidosis, although these could not be considered diagnostic. Urinary excretion of calcium is high in all cases of hypercalcemia (despite inappropriate calcium resorption stimulated by PTHrP). The renal phosphate threshold is low in the presence of PTHrP, indicating a renal phosphate leak, and significant hypophosphatemia may result after the treatment of hypercalcemia.

The serum immunoreactive PTH is low or undetectable unless the primary site of malignancy is the parathyroid gland itself. Vitamin D metabolites are also frequently low in most cases of hypercalcemia, despite the fact that PTHrP is capable of stimulating the renal 1-a hydroxylase in animal models. The reason for this paradox is not clear, although it has been suggested that tumors may secrete an independent inhibitor of 1-a hydroxylase (55). Measures of osteoblastic function, such as alkaline phosphatase and bone gla-protein (osteocalcin), have little to offer in the diagnosis of hypercalcemia. Although plain radiography and isotope bone scans may help with other aspects of management, they are of little use in the diagnosis and management of hypercalcemia in the face of established disease.

Grading Hypercalcemia in Malignant Disease

The appearance of hypercalcemia in patients with malignant disease is a poor prognostic indicator in most clinical situations. The major exception is in patients recently initiated on tamoxifen citrate therapy for breast cancer. The mechanism by which tamoxifen citrate causes hypercalcemia is unclear. It is likely, however, that prostaglandins play a central role in this phenomenon of tamoxifen citrateinduced “flare,” which is frequently associated with bone pain and subsequently a response of the tumor to therapy.

From a practical point of view, it is important to note that the development and severity of symptoms do not correlate well with the serum calcium level. Indeed, patients with symptoms readily relatable to hypercalcemia should be classified and treated as severe, independent of the absolute calcium level. An observation that is frequently made but poorly understood is that patients with tumor-induced hypercalcemia often have greater symptomatology for any given rise in calcium level compared with patients with primary hyperthyroidism.

Patients with a corrected serum calcium level below 3.0 mmol/l (<12 mg/dl) who are asymptomatic can be considered as having mild hypercalcemia. This condition may have been detected as part of the routine biochemical work up in patients with tumor types known to predispose to hypercalcemia. Often these patients are being monitored in the outpatient clinic. With the new development of hypercalcemia, it is important to reevaluate the current antineoplastic therapy because this complication may be an early indication of a diminishing response. Immediate treatment of the hypercalcemia may not be indicated, but it is important to remember that the natural history is for the hypercalcemia to worsen unless a tumor response can be obtained or some intercurrent illness that has precipitated the hypercalcemia can be reversed.

In asymptomatic patients with a serum calcium of 3.0–3.5 mmol/l (12–14 mg/dl), the situation is more serious. Any event that induces volume depletion or reduces the glomerular filtration rate, including the institution of medication such as nonsteroidal anti-inflammatory agents, may be enough to lead to severe hypercalcemia. Patients with a corrected serum calcium concentration of greater than 3.5 mmol/l (>14 mg/dl) require urgent treatment, as do patients with symptomatic hypercalcemia.

TREATMENT OF HYPERCALCEMIA

General Considerations

It is possible to lower the serum calcium concentration in nearly all patients with tumor-induced hypercalcemia. The basic principles to be used are relatively simple. Most patients with hypercalcemia are sodium- and waterdepleted and require aggressive rehydration. The best therapeutic strategy is one directed at removing the cause of the hypercalcemia, including the judicious use of surgery, radiotherapy, and chemotherapy. Hypercalcemia is maintained by two main pathways. Enhanced osteoclastic bone resorption is present in virtually all cases of hypercalcemia. Specific antiresorptive therapy is available and should be used early in the management of the complication. Increased renal reabsorption of calcium is present in cases in which PTHrP is acting on the kidneys. In an attempt to offset this problem, high urine volume should be maintained, but direct antagonism of the effects of PTHrP on the kidney is not readily available.

Dietary restriction of calcium-containing products seems intuitively appropriate; however, it is important to remember that, except where the mechanism of the hypercalcemia is thought to be vitamin D–dependent, gastrointestinal absorption of calcium is very low. Every effort should be made to maintain the mobility of the

patient, and medications predisposing to hypercalcemia, such as thiazide diuretics and vitamin D and A supplements, should be avoided. Table 34-2 summarizes potential options for the management of hypercalcemia in malignant disease.

Treatment	Dose	Response[b]	Comments
Saline diuresis	3 l/d i.v. (or more)	Rarely complete	Important component of therapy for severe hypercalcemia due to accompanying dehydration (see text).
Furosemide	40–80 mg/d p.o. or i.v.	See comment	Useful for maintaining diuresis in patients receiving aggressive hydration (especially enteral) to avoid fluid overload.
Zoledronic acid	4 mg i.v. over ≥15 min	Approximately 80%	Potential for longer duration of response. Short infusion times facilitate outpatient use. Renal dysfunction with dose escalation or rapid infusion times.
Pamidronate disodium	60–90 mg i.v. over 4 h	60–90%	Highly effective, well tolerated, convenient for outpatient administration.
Etidronate disodium Gallium nitrate Mithramycin (Mithracymin)	7.5 mg/kg/d i.v. over 2 h for 3–5 d 200 mg/m² for 5 d i.v. 25 μg/kg i.v. (approximately 1.5–2.0 mg)	25–45% 75–80% Approximately 80%	Widely infused only. Inconvenient schedule, potentially nephrotoxic. Teratogenic, anticant. Increased response with repeated daily dosing but with increased myelosuppression, hepatic and renal toxicity.
Calcitonin	4 MRC U/kg s.c. q2–2h to 8 MRC U/kg s.c. q8h (approximately 300–400 U)	See comment	Rapid effect but seldom complete normalization of serum calcium. Tachyphylaxis.
Glucocorticoids	Prednisone, 40–100 mg/d or equivalent.	See comment	Effective in hematological malignancies with cytokine or $1,25-(OH)_2D_3$-mediated hypercalcemia and hormone-induced skeletal flare response.
Antiprostaglandins	Indomethacin, 75–100 mg/d or equivalent	Rare	Little value.
Inorganic phosphorus	1 g/d in divided doses titrated to 2–3 g/d	Maintenance range	Dose-limiting diarrhea.

MRC, Medical Research Council.
[a]Currently approved in the United States.
[b]Normalization of albumin-adjusted serum calcium.

TABLE 34-2. THERAPEUTIC OPTIONS FOR HYPERCALCEMIA[a]

Establishing Treatment Goals

When embarking on the treatment of hypercalcemia in malignant disease, it is important to have clear goals in mind. If no therapeutic intervention directed at the underlying malignancy is available or planned, patient survival is short-lived. Ralston et al. (56) reported a median survival time of 30 days for 100 hypercalcemic patients in whom no antitumor therapy was available; indeed, all patients in this group had died by 120 days. These data are similar to those presented by Nussbaum et al. (3), who reported a median survival of 1.4 months. If such a patient is relatively asymptomatic or already obtunded, it may be that aggressive attempts to normalize calcium levels are unwarranted. In most patients with symptomatic hypercalcemia, however, the mental status abnormalities and confusion, as well as the chronic nausea and constipation, are so troublesome as to make palliative antihypercalcemic therapy worthwhile. Indeed, even in cases in which symptoms may be severe, normalization of serum calcium and resolution of symptoms can be achieved with appropriate therapy, which may allow a terminally ill patient another chance to see and speak with family members and clergy, attend to legal matters, and complete unfinished business. We find that early consultation with the palliative care team is extremely useful in these circumstances, as long-term antihypercalcemia therapy can be given on an outpatient basis or even in the patient's home.

Extracellular Fluid Volume Expansion

The combined effects of anorexia, vomiting, compromised mental status, and nephrogenic diabetes insipidus render most patients with hypercalcemia significantly volumedepleted, as much as 5–10 liters. Under these circumstances, the glomerular filtration rate is reduced and inappropriate calcium retention occurs as the kidneys attempt to conserve sodium. Normal saline solution should be infused, initially as rapidly as the patient's cardiac status will tolerate. Thereafter a saline infusion should be continued until normocalcemia is restored by other means. If a state of mild volume overload can be induced, the fractional excretion of calcium can be increased significantly. Hosking et al. (57) demonstrated that it was possible to produce a mean drop in calcium concentration of 0.6 mmol/l (2.4 mg/dl) in their study of 16 hypercalcemic patients. The authors concluded that most of the calciumlowering effect was based on improving the glomerular filtration rate and increasing the fractional excretion of sodium, permitting appropriate off-loading of calcium by the kidneys. They noted three patients in whom the tubular resorption rate of calcium appeared fixed. Presumably, those patients were reabsorbing calcium under the influence of PTHrP. Although restoration of fluid volume rarely restores the calcium level to the normal range—the mean postrehydration value in Hosking's study was 3.24 mmol/l (12.8 mg/dl)—a failure to rehydrate the patients certainly compromises the efficiency of other therapeutic maneuvers.

Antiresorptive Therapy

Enhanced osteoclastic bone resorption, either driven hormonally by the effects of PTHrP or in a paracrine fashion by factors released from tumor deposits within bone, is the final common pathway in the genesis of hypercalcemia in malignant disease. It is of little surprise, therefore, that osteoclast inhibitors are effective in the treatment of hypercalcemia. In the last decade, the introduction of newer, more effective, and less toxic antiresponsive medications have replaced more conventional methods for the management of the hypercalcemia of malignancy.

Bisphosphonates

The bisphosphonates are structural analogs of pyrophosphate in which the P-O-P bond is replaced by a P-C-P bond that is resistant to enzymatic cleavage by endogenous pyrophosphatases. The commonly available bisphosphonates are etidronate disodium, clodronate, and the aminobisphosphonates, pamidronate disodium and alendronate.

Several newer bisphosphonates have undergone clinical trials in patients with hypercalcemia including risedronate sodium, ibandronate, and zoledronic acid.

Bisphosphonates share poor and unpredictable oral bioavailability. Furthermore, the bioavailability is reduced almost to zero if they are ingested with food. In the setting of symptomatic hypercalcemia of malignancy, the intravenous route is preferred because nausea and vomiting are such frequent occurrences. Once absorbed, approximately half of the ingested dose is excreted unchanged in the urine. Bone mineral has a high affinity for bisphosphonates, which are rapidly adsorbed onto the bone surface (58). Although the bulk of any absorbed bisphosphonate is rapidly relocated to the bone, this is nonhomogeneous, with most of the bisphosphonate located in areas of highest bone turnover.

The method by which bisphosphonates inhibit osteoclast function is unclear, and it is likely that several mechanisms are involved. The high-affinity adsorption of bisphosphonates to hydroxyapatite crystals suggests that an important physicochemical process may operate. Bisphosphonates affect the ionic composition of the hydration layer that normally surrounds bone crystals (59). The altered concentrations of calcium and phosphate in this microenvironment may be responsible for the relative stability induced by the bisphosphonates.

Osteoclast attachment to bone may be reduced in the presence of bisphosphonates. Carano et al. (60) demonstrated a 30% reduction in bone binding by osteoclasts in tissue culture in the presence of etidronate disodium, clodronate, and pamidronate disodium. An inhibition of osteoclast acid hydrolases also has been described (61). Given that these enzymes are so important in bone resorption, this may account in part for some of the effects of the bisphosphonates. Other effects suggested for bisphosphonates include a reduction in osteoclast progenitor maturation, interference with energy-producing enzymes, and a direct cytotoxic effect on osteoclasts.

Aminobisphosphonates

Pamidronate disodium was the first aminobisphosphonate licensed for clinical use. It is effective in restoring normocalcemia (Fig. 34-1), with expected response rates of the order of 90% (62). Although an early dose–response study suggested little advantage to increasing the dose beyond 0.25 mg/kg, a large multicenter trial in the United States has shown that a single starting dose of 90 mg may be optimal (3). In initial studies, pamidronate disodium was given in divided doses over a period of several days; however, the normocalcemic effect can be achieved with single-dose therapy (63). Dodwell et al. (64) studied more rapid infusion rates and found that the drug can be given safely and efficaciously over a 2-hour period.

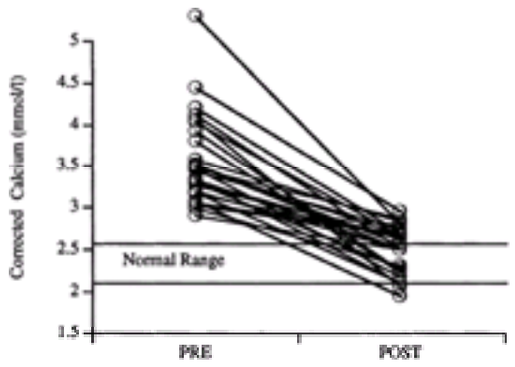

FIGURE 34-1. Effect of pamidronate disodium therapy on 30 hypercalcemic patients. [From Morton AR, Cantrill JA, Craig AE, et al. Single dose versus daily intravenous aminohydroxypropylidene bisphosphonate (APD) for the hypercalcaemia of malignancy. *BMJ* 1988;296:811, with permission.]

Pamidronate disodium was shown to be the most effective of the bisphosphonates available in 1989 (65). Another study has confirmed the superiority of pamidronate disodium to clodronate using higher doses of each drug. Not only was the complete response rate greater for pamidronate disodium as compared to clodronate, but the duration of the response was significantly longer (66). In a comparative randomized, crossover study, Thürlimann et al. (67) demonstrated that a single intravenous dose of 60 mg pamidronate disodium was more effective than a dose of 20 µg/kg of plicamycin. No primary failures occurred in the pamidronate disodium–treated group, and those primary failures in the plicamycin-treated group became normocalcemic when treated with pamidronate disodium. Although one randomized study comparing 30 mg with 90 mg pamidronate disodium failed to show a significant difference in therapeutic efficacy (68), other prospective and retrospective evaluations identified a clear dose–response relationship over this dose range (3,69). This may have important clinical implications, particularly for patients with severely elevated serum calcium levels in whom higher doses may be necessary to achieve normocalcemia. For most patients, 60 mg pamidronate disodium appears adequate to restore the serum calcium to normal. In the United States, initial approval restricted pamidronate disodium administration to a 24-hour intravenous infusion. Subsequently, the approval was liberalized to allow shorter duration infusions over 4 hours, thus facilitating outpatient or home administration.

Alendronate disodium is an aminobisphosphonate that is routinely used in the management of osteoporosis. Like other bisphosphonates, it is a powerful antihypercalcemic agent (70). A dose–response and duration of response study demonstrated that normalization of corrected calcium can be expected in approximately 90% of patients given 10 mg of this agent intravenously over 2 or 24 hours (71). As with pamidronate disodium, the efficacy and safety of a rapid infusion rate lend itself to outpatient management.

Ibandronate is an amino-substituted bisphosphonate that is approximately 50 times more potent than pamidronate disodium in animal models of stimulated osteoclast activity. Two dose–response studies of ibandronate have confirmed its efficacy in the treatment of hypercalcemia in malignant disease (72,73). Ralston et al. found a 77.4% complete response rate to a dose of 6 mg infused over 2 hours (73). This response rate is similar to that found in the studies of pamidronate disodium, but the two agents have not yet been compared in a randomized trial.

Other Bisphosphonates

The first commercially available bisphosphonate, etidronate disodium, has a relatively weak antihypercalcemic effect. Randomized studies proved it to be less effective than pamidronate disodium, clodronate, or gallium nitrate (65,74).

Clodronate is a highly efficacious bisphosphonate. The appearance of three cases of acute leukemia in 664 patients in a multicenter study involving its use in the United States led to the temporary withdrawal of this agent (75). Despite this concern, clodronate has continued to be used both intravenously and orally for the management of hypercalcemia and other neoplastic effects on bone in Europe and Canada. It is an effective agent in restoring normocalcemia, with a reported response rate of 89% (24 of 27 patients) in one study of patients receiving 100–300 mg/day for 3–10 days (76). Oral clodronate also appears able to induce a normocalcemic response (77). In the clinical situation of the acute management of hypercalcemia, the intravenous route is preferred; however, long-term treatment with oral clodronate may be a useful therapy to maintain normocalcemia. In direct comparative studies (65,66), clodronate was less effective than pamidronate disodium both in frequency and duration of patient response.

Zoledronic acid is a new nitrogen-containing heterocyclic imidazole bisphosphonate that is estimated to be approximately 100 times more powerful than pamidronate disodium. An early dose-finding study indicated that the effective dose was approximately 0.02–0.04 mg/kg (78). An analysis of randomized, controlled clinical trials has demonstrated the superiority of 4 and 8 mg of zoledronic acid over 90 mg pamidronate disodium both in terms of complete response rate for normalization of corrected calcium levels and duration of antihypercalcemia response (79).

Effect of Tumor Type on Response to Bisphosphonates

Evidence suggests that cases of hypercalcemia that are mediated mainly by PTHrP may be more resistant to antiresorptive therapy (80,81). Decreased responsiveness to pamidronate disodium was observed when the hypercalcemia was associated with elevated levels of PTHrP (82). In a study of the efficacy of ibandronate (73), tumor type was clearly identified as a predictor of response to therapy. Patients with breast cancer or hematological malignancies were statistically more likely to respond to ibandronate than those with other tumor types. In a study with zoledronic acid, the complete response rate to 4 and 8 mg was lower in patients with elevated PTHrP levels, although this did not reach statistical significance (79). The implications are that patients with hypercalcemia due to tumor types that are associated with PTHrP production are likely to be less responsive to lower doses of bisphosphonate therapy.

Duration of Response to Bisphosphonate Therapy

The true duration of response to bisphosphonates is difficult to determine. The mortality rate in this group is high, and many patients die without becoming hypercalcemic again. Furthermore, effective antitumor therapy is introduced whenever possible, confounding the issue of time to recurrence of hypercalcemia. For pamidronate disodium the median duration of normocalcemia was found by Thiébaud et al. to be 35 days (83), significantly longer than the 9–13 days reported by Nussbaum et al. (3) and the 18 days found in the large comparative study with zoledronic acid (79). The median response duration for ibandronate was approximately 12 days regardless of 2-, 4-, or 6-mg dose (73). For zoledronic acid, the response duration was 32 days for the 4 mg dose and 43 days for 8 mg dose (79).

Side Effects of Bisphosphonates

Bisphosphonates have a wide therapeutic index, making them a good choice of agent for patients with advanced malignancy. Oral formulations tend to be associated with gastrointestinal intolerance, which may be dose limiting. This is not usually a problem in the acute setting, in which intravenous therapy is indicated, but may limit their role for chronic administration. Rapid intravenous infusions of etidronate disodium and clodronate have been associated with the deterioration of kidney function in patients with myeloma and preexisting renal compromise (84). Renal adverse events, including significant elevations in serum creatinine, were noted infrequently in all groups of patients in the zoledronic acid comparison study with pamidronate disodium (79). Low-grade pyrexia is noted in 10–15% of patients. Hyperphosphatemia is noted with etidronate disodium therapy, but hypophosphatemia is also seen with clodronate, pamidronate disodium, ibandronate, and zoledronic acid treatment. The mechanisms of phosphate imbalance are unclear and are rarely of clinical significance. Ocular adverse reactions occasionally may be observed, including anterior uveitis, scleritis or episcleritis, and nonspecific conjunctivitis (85).

Calcitonin

The hypocalcemic effects of calcitonin are due in part to a direct inhibition of osteoclast function. Normocalcemia is rarely restored with this agent; however, its actions are rapid, and it can be combined effectively with one of the powerful bisphosphonates (86,87). This may be particularly useful in patients in whom neurological symptoms due to the hypercalcemia are troublesome.

An additional advantage for calcitonin is that it induces a mild degree of renal calcium wasting that begins promptly after administration (88). Unfortunately, tachyphylaxis develops within 2–3 days due to down-regulation of calcitonin receptors, and although this effect may be reduced by the simultaneous administration of corticosteroids (89), the effects of calcitonin are not long lasting. The suggested dose is 4 Medical Research Council U/kg every 12 hours by injection, although doses as high as 8 MRC U/kg every 6 hours may be used. A test dose of 1 MRC U intradermally has been recommended to identify allergic individuals. An alternative route of

administration is by rectal suppository (90).

Gallium Nitrate and Plicamycin (Mithramycin)

Gallium nitrate is an effective antihypercalcemic agent, the mechanism of action of which is unclear (91). Its utility is limited by the fact that the most effective dose is a continuous infusion of 200 mg/m^2 given daily for 5 days.

Plicamycin, formerly mithramycin, is an antitumor antibiotic that has antiosteoclastic activity. Its mechanism of osteoclast inhibition is incompletely understood, but it appears to interfere with mRNA synthesis within the cells (92). Although effective in restoring normocalcemia, much concern has been raised over the potential side effects of marrow, hepatic, and renal toxicity. In fact, an infusion of 25 µg/kg over 4–6 hours is approximately one-tenth the dose at which those side effects are commonly seen, but restores normocalcemia in approximately 40% of patients (93). The onset of the hypocalcemic effect is rapid with plicamycin, being evident within the first 24 hours. As with other agents, the individual duration of response is unpredictable, and close monitoring is necessary to avoid serious rebound hypercalcemia. Plicamycin has been used with success in patients with recalcitrant hypercalcemia.

Prostaglandin Synthesis Inhibitors

Given the fact that some tumor types could cause hypercalcemia in association with the high renal excretion of prostaglandin synthetase inhibitors, it was hoped that these agents would be a powerful addition to the oncologist's armamentarium. Unfortunately, responses to these agents are relatively rare.

Other Therapy

Furosemide

The loop diuretic furosemide continues to be used frequently in the management of hypercalcemia. Evidence for its effectiveness comes from a study in 1970 by Suki et al. (94), who used high doses of furosemide, approximately 80–100 mg every 2–4 hours, to achieve their effect. Generally speaking, this regimen is impractical because intensive fluid and electrolyte monitoring with appropriate replacement is required. The use of diuretics before establishing mild hypervolemia may even be counterproductive by enhancing the renal resorption of calcium linked to sodium from the proximal convoluted tubules.

Furosemide should be limited to patients in whom aggressive fluid replacement can potentially induce congestive cardiac failure. It has no place in the chronic management of hypercalcemia.

Corticosteroids

Glucocorticoids are another group of agents that are frequently used in the management of hypercalcemia of malignancy despite evidence that their role is very limited (Fig. 34-2) (95,96). Certain tumor types are inherently responsive to glucocorticoid therapy, including multiple myeloma and lymphoma. Osteolytic cytokines mediating the hypercalcemia may be inhibited by corticosteroids, and these agents also may be useful in managing the flare response occasionally seen after initiating hormonal therapy for breast cancer. In cases in which hypercalcemia is mediated by excessive 1,25-$(OH)_2D_3$, glucocorticoids may have an antagonistic effect on calcium absorption from the gut.

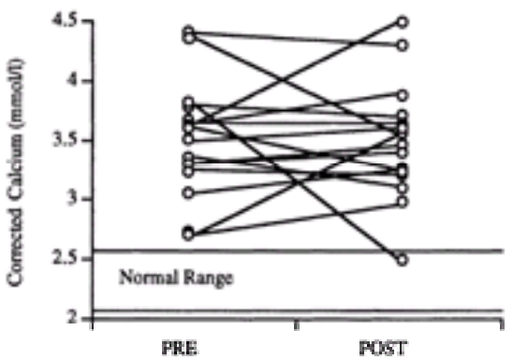

FIGURE 34-2. Effect of varying doses of corticosteroids on ten hypercalcemic patients with solid tumors. (From Thalassinos NC, Joplin GF. Failure of corticosteroid therapy to correct the hypercalcemia of malignant disease. *Lancet* 1970;2:537, with permission.)

Phosphate

Oral phosphate, with its chelating action on intestinal calcium, may be useful as an adjunct for the long-term management of hypercalcemia. The dose-limiting side effect is diarrhea.

Experimental Agents

Established antitumor agents such as cisplatinum have been used in an attempt to control hypercalcemia. The total dose used by Lad et al. (97) in their study of 13 patients with hypercalcemia was 100 mg/m^2. Aside from its antineoplastic effects, the mechanism of hypopcalcemia with cisplatinum is unclear. It is recognized that this agent is toxic to the loop of Henle in the kidney, and this may represent the source of calcium wasting.

Ethiofos (WR-2721) is a myeloprotective agent that appears able to suppress PTH secretion and bone resorption. Although its effects on PTHrP release are currently unknown, ethiofos could have great potential if able to suppress the release of this tumor product. It is associated with mild nausea and vomiting as well as potentially troublesome hypotension. Clinical experience in the management of hypercalcemia with this agent remains limited.

Osteoprotegrin is an autocrine substance secreted in the bony milieu that appears to act by binding ODF, thus preventing the differentiation of osteoclasts (98). Early animal studies suggest that it is a potent antihypercalcemic agent, even in tumors expressing PTHrP (99).

SUMMARY

Hypercalcemia of malignancy is a common problem. If promptly recognized, useful palliation may be made available. Strategies aimed at removing or reducing the underlying tumor burden should be sought. Where no effective therapy for the tumor is available, patients are normally in the last few weeks to months of their lives. A thoughtful decision should be made before embarking on antihypercalcemic therapy in terminally ill patients who may be relatively asymptomatic. Volume repletion is the mainstay of therapy, followed by the use of antiresponsive medications. The aminobisphosphonates are effective, safe agents in this regard. They may be given over short infusion times, which can allow therapy to take place in the outpatient or home setting. Individualization of therapy is required because the duration of response to any of the hypercalcemic agents is relatively unpredictable.

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35

METABOLIC DISORDERS IN THE CANCER PATIENT

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Endocrine disorders occur in persons with advanced malignancy under various circumstances. Cancer may produce effects through the excess production of hormones, cytokines, and growth factors, the so-called “paraneoplastic syndromes” (Table 35-1). Conversely, the cancer or its metastases may interfere with the normal function of endocrine organs, resulting in hormone-deficiency states. Most commonly, patients have a metabolic disorder such as diabetes, thyroid dysfunction, or hyperparathyroidism that predates the diagnosis of their malignancy or is diagnosed incidentally during the course of their malignancy. This chapter discusses the most common paraneoplastic syndromes and hormone-deficiency states associated with malignancy, as well as the management of diabetes and thyroid disease in the cancer patient.

Syndrome	Tumor type
Inappropriate antidiuresis (hormone vasopressin)	Lung cancer, all types
Cushing's syndrome (adrenocorticotropic hormone, corticotropic hormone)	Lung cancer, all types
Hypocalcemia	Bone metastases
Hypophosphatemia ("phosphatonin")	Mesenchymal tumors
Hyperthyroidism (human chorionic gonadotropin)	Lung cancer, all types
Gynecomastia (estrogens, follicle-stimulating hormone, lutenizing hormone)	Lung cancer, all types
Calcitoninemia (calcitonin)	Medullary carcinoma of the thyroid, lung cancer, breast cancer
Acromegaly (growth hormone, growth hormone releasing hormone)	Carcinoids, pheochromocytoma, pancreatic cancer

TABLE 35-1. COMMON PARANEOPLASTIC SYNDROMES

ENDOCRINE PARANEOPLASTIC SYNDROMES

Inappropriate Antidiuresis

The differential diagnosis of hyponatremia in the cancer patient is similar to that in the general population and includes hepatic and cardiac failure, renal disease, overdiuresis, factitious hyponatremia associated with hyperglycemia, and other conditions. In the syndrome of inappropriate antidiuretic hormone (SIADH), hyponatremia results from the overproduction of vasopressin (AVP) by the posterior pituitary gland in response to a stimulus by tumor cells, by the actual production of AVP or AVP-like peptides by tumor cells, or as a side effect of medications able to stimulate AVP production.

Epidemiology

The most common malignancies causing SIADH are small cell lung cancer and carcinoid tumors; SIADH also is seen with cancers of the esophagus, pancreas, duodenum, colon, adrenal cortex, prostate, thymomas, and lymphomas. In one series, the incidence of clinically significant SIADH was 9% among 523 small cell lung cancer patients. A larger fraction of patients had milder abnormalities in AVP metabolism without hyponatremia. Thus, approximately one-half of patients had abnormal renal handling of water loads that were subclinical (1,2). Another study found that 41% of patients with all types of lung cancers and 43% of colon cancer patients had significantly elevated levels of AVP without evidence of clinically significant SIADH (3).

Clinical Features

The clinical features of hyponatremia depend on the degree of hyponatremia and the rate of its development. Most patients with chronic hyponatremia are asymptomatic. Generally, symptoms do not occur until the serum sodium falls below 115–120 mEq/l (4). When they occur, the signs and symptoms of SIADH are caused by water intoxication (i.e., hypoosmolality and hyponatremia) and are manifested by confusion, lethargy, seizures, or coma. Occasionally, patients may present with focal neurological deficits.

Diagnosis

Because most cases of SIADH are asymptomatic, the diagnosis is usually first suspected by noting a low serum sodium on routine chemistries. Other causes of hyponatremia, such as hypovolemia, hypervolemia (occurring in renal or hepatic disease or cardiac failure), hypothyroidism, and adrenal insufficiency, must be excluded before the diagnosis of SIADH can be considered. Urine chemistries show urinary osmolality greater than serum osmolality and a high urinary sodium concentration (Table 35-2). Medications commonly used by cancer patients associated with SIADH include morphine sulfate, vincristine sulfate, cyclophosphamide, phenothiazines, and tricyclic antidepressants. Most drugs cause SIADH by stimulating posterior pituitary secretion of AVP.

Plasma sodium level below 135 mEq/l
Urine osmolality greater than serum osmolality
Elevated urine sodium (>20 mEq/l)
Normal extracellular fluid volume
Rule out other causes of euvolemic hyponatremia

TABLE 35-2. DIAGNOSIS OF SYNDROME OF INAPPROPRIATE ANTIDIURESIS

Treatment

The treatment of SIADH is determined by the rate of development of hyponatremia and by the presence of neurological sequelae. If the patient is symptomatic and has a serum sodium level below 130 mEq/L, fluid restriction to 800–1000 ml per 24 hours is effective in slowly raising serum osmolality over a period of 3–10 days. Acute hyponatremia with neurological symptoms has a mortality rate of 5–8% and warrants more aggressive treatment. For patients with more severe hyponatremia, the intravenous administration of hypertonic saline (3% saline at a rate of 0.1 mg/kg per minute) and furosemide may be necessary (5). Careful monitoring of vital signs and urinary losses of sodium and potassium is indicated. Rapid correction of severe hyponatremia has been associated with central pontine myelinosis, which presents with quadriparesis and bulbar palsy 1–2 days after correcting hyponatremia. A safe rate of correction in severe hyponatremia is 0.5–1.0 mEq/l per hour until the sodium concentration reaches 125 mEq/l (6,7).

Fluid restriction is not feasible in some patients who require long-term treatment of SIADH. In these patients, medications, including demeclocycline hydrochloride, lithium carbonate, and urea, have been tried. Demeclocyline is the drug of choice and causes partial nephrogenic diabetes insipidus by inhibiting the formation of AVP-induced cyclic adenosine monophosphate in distal tubules. It is initially administered orally in divided doses of 900–1200 mg/day and then reduced to maintenance doses of 600–900 mg/day. Side effects are mainly gastrointestinal, although hypersensitivity and nephrotoxicity can occur. Similar to demeclocycline hydrochloride, lithium carbonate also causes a reversible, partial form of nephrogenic diabetes insipidus but is less effective. Urea acts as an osmotic diuretic and allows the patient to maintain a normal fluid intake. Urea can be administered intravenously or orally. When given by mouth, the usual dosing is 30 g of urea dissolved in 100 ml of orange juice or water once daily (8).

Cushing's Syndrome

Endogenous Cushing's syndrome is due to one of three causes: overproduction of glucocorticoid by a primary adrenal neoplasm, excessive production of adrenocorticotropic hormone (ACTH) by a pituitary adenoma, or a paraneoplastic syndrome in which either ACTH or corticotropic hormone (CRH) are produced ectopically by the tumor. A number of tumors are capable of producing ACTH, its prohormone “big ACTH,” or pro-opiomelanocortin (POMC) (Table 35-3). The POMC gene is located at *p23* on the short arm of chromosome 2 near N-*myc* oncogene at *p24*. The expression of the POMC gene normally is influenced by glucocorticoids, which suppress transcription, and CRH, which stimulates transcription via cyclic adenosine monophosphate. The activation of alternative steroidinsensitive promoters may result in ectopic ACTH production that is insensitive to glucocorticoid suppression. Pituitary cells and some tumors produce the normal 1200-base mRNA transcript; however, some nonpituitary tissues produce either a larger or smaller POMC mRNA transcript. Alternative posttranscription processing of POMC gives rise to a large number of biologically active peptides in addition to ACTH. These include pro-ACTH and a number of different peptides containing melanocyte-stimulating hormone (MSH) (a-MSH, ACTH, pro-ACTH, b-MSH, t-lipotropin, b-lipotropin, t-MSH, N-POMC, pro-t- MSH), all of which can lead to generalized hyperpigmentation (9,10). Radioimmunoassays differ in their abilities to detect aberrant ACTH. The immunoradiometric assay for ACTH is able to distinguish between ACTH and its larger precursors, pro-ACTH, and POMC (11).

Small cell lung carcinoma
Thymoma
Pancreatic islet-cell tumor
Carcinoid tumors (lung, gut, pancreas, ovary)
Medullary carcinomas of the thyroid
Pheochromocytomas

TABLE 35-3. TUMORS ASSOCIATED WITH ECTOPIC ADRENOCORTICOTROPIC HORMONE/CORTICOTROPIC HORMONE SYNDROME

Epidemiology

Ectopic ACTH is most frequently secreted by lung carcinomas. A number of other tumor types are also capable of producing this syndrome (Table 35-3). In the general population, approximately 65% of patients with Cushing's syndrome have pituitary adenomas producing ACTH (Cushing's disease), 20% have primary adrenal tumors, and 14% have ectopic ACTH. Therefore, ectopic ACTH production is the least common of the three major causes in the general population.

Clinical Features of Ectopic Adrenocorticotropic Hormone Syndrome

Manifestations of the ectopic ACTH syndrome include hypokalemia, hyperglycemia, edema, muscle weakness (especially proximal) and atrophy, hypertension, and weight loss. Features typically seen in long-standing pituitary or adrenal Cushing's syndrome (e.g., central obesity, plethoric facies, cutaneous striae, “buffalo hump,” and hyperpigmentation) are less common in highly malignant tumors such as small cell lung carcinoma but occur more frequently in more indolent tumors such as carcinoids, thymomas, and pheochromocytomas.

Diagnosis

The biochemical diagnosis of Cushing's syndrome is suggested by an elevated 24-hour urinary-free cortisol (>100 µg/24 hours). The other principal screening test is the overnight low-dose dexamethasone suppression test. The test is positive when 1 mg of dexamethasone given at midnight is unable to suppress the following 8:00 a.m. cortisol to less than 5 µg/dl. Failure of cortisol to suppress after high-dose dexamethasone (8 mg at midnight) suggests either ectopic ACTH or a primary adrenal tumor (12). These two are differentiated by measuring plasma ACTH. In primary adrenal tumors, ACTH levels are below 20 pg/ml, whereas in ectopic ACTH levels are generally greater than 100 to 200 pg/ml and frequently are elevated above 1000 pg/ml. Inferior petrosal sinus sampling of ACTH is useful in confirming the diagnosis of pituitary Cushing's syndrome (13), but it is rarely indicated in the patient with advanced malignancy secreting ectopic ACTH.

Difficulties arise in differentiating those rare tumors producing ectopic CRH from the more common ectopic ACTH production; CRH stimulates release of pituitary ACTH. The clinical presentation and biochemical results are identical for ectopic CRH and ACTH. The prognosis and therapy are identical for the two disorders.

Treatment of Ectopic Adrenocorticotropic Hormone Syndromes

Where possible, the treatment of ectopic ACTH syndrome should be directed primarily at the tumor. Palliative treatment of Cushing's syndrome involves inhibition of steroid synthesis. Drugs successfully used include aminoglutethamide, metyrapone, mitotane, ketoconazole, and octreotide acetate (14). Rarely, bilateral adrenalectomy is considered.

Aminoglutethamide blocks the first step in cortisol biosynthesis. At higher doses, it inhibits production of glucocorticoids, mineralocorticoids, and androgens, whereas at lower doses it primarily inhibits the conversion of androgens to estrogens, contributing to its efficacy in the treatment of postmenopausal breast cancer. At the higher doses required to treat ectopic ACTH syndrome, many patients experience sedation, ataxia, and skin rashes. Metyrapone inhibits 11 b-hydroxylase and 18-hydroxylase, resulting in adrenal atrophy and necrosis. It is a toxic drug with significant gastrointestinal side effects, including anorexia, nausea, vomiting, and diarrhea, and central nervous system toxicity, including lethargy and somnolence. For these reasons, it is used as second-line therapy.

Ketoconazole acts mainly on the first step of cortisol biosynthesis but also inhibits the conversion of 11-deoxycortisol to cortisol. It can cause rare but significant

reversible hepatotoxicity and is associated with nausea and vomiting.

Octreotide acetate, a long-acting analog of somatostatin, can reduce ectopic ACTH secretion. It must be injected, is expensive, and is only partially effective in most patients. The efficacy of these treatments can be monitored by 24-hour urine cortisol measurements. As levels return to normal and then fall below normal, replacement with glucocorticoids and mineralocorticoids in physiological doses similar to patients with Addison's disease is frequently necessary. In cases of stress, these patients require stress doses of glucocorticoids (e.g., hydrocortisone 100 mg intravenously every 8 hours).

Hypocalcemia

Hypocalcemia is an uncommon paraneoplastic syndrome occurring primarily in patients with bony metastases. It occurs most commonly in association with osteoblastic metastases of the breast, prostate, and lung; its incidence is approximately 16% (15). Tetany is a rare complication of tumor-associated hypocalcemia. The etiology of the hypocalcemia is not understood. Ectopic calcitonin secretion from the underlying tumor has been rarely implicated.

Oncogenic Hypophosphatemic Osteomalacia

Oncogenic hypophosphatemic osteomalacia, an acquired form of adult-onset, vitamin D-resistant rickets, is associated with mesenchymal tumors, often benign, that occur in soft tissues or bone (16). These tumors are also referred to as *ossifying mesenchymal tumors*, *giant cell tumors of bone, sclerosing hemangioma*, or *cavernous hemangioma*. This syndrome has been rarely reported with other cancers, such as lung and prostate. The clinical syndrome can precede the discovery of the tumor by several years. Clinical and laboratory features include osteomalacia, severe phosphaturia, renal glycosuria, hypophosphatemia, normocalcemia (normal parathyroid hormone levels), and increased alkaline phosphatase. The proposed mechanisms for this syndrome include inhibition of the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D and a substance produced by the tumor with a phosphaturic effect “phosphatonin.” A candidate gene for “phosphatonin” has recently been described— fibroblastic growth factor 23 (17). Treatment is directed at surgical resection of the underlying tumor. When this is not possible, treatment with high doses of vitamin D and phosphate is often required.

Hyperthyroidism

Human chorionic gonadotropin (hCG) most commonly is secreted by trophoblastic or germ cell tumors (18). Because of its evolutionary homology with thyroid stimulating hormone (TSH), hCG has intrinsic thyrotropic action. Overt hyperthyroidism usually occurs with large tumors secreting large quantities of hCG, such as gestational trophoblastic disease (e.g., choriocarcinoma, hydatidiform mole) and testicular tumors. The hyperthyroidism resolves with surgical resection of the underlying tumor. When necessary, treatment of the hyperthyroidism is achieved by using antithyroid drugs such as propylthiouracil or methimazole.

Gynecomastia

Gynecomastia is defined as palpable breast tissue in men (19) and may be caused by drugs that lower testosterone levels (20), including alkylating agents, vinca alkaloids, and nitroureas. Antiemetics, such as metoclopramide and phenothiazines, may produce gynecomastia by stimulating prolactin production. Alternatively, tumor production of gonadotropins or estrogens may result in gynecomastia; these include adrenal and testicular tumors and hepatomas. Tumors that produce hCG can stimulate estrogen production by interstitial and Sertoli cells of the testes, resulting in gynecomastia. The approach to the treatment of gynecomastia includes treatment of the underlying tumor and, if implicated, cessation of drugs known to cause gynecomastia.

Treatment of gynecomastia with antiestrogens and androgens such as tamoxifen citrate, clomiphene citrate, topical dishydrotestosterone, and danazol is generally unsuccessful. For more severe cases, long-term management with liposuction and subcutaneous mastectomy may be necessary. Low-dose radiation therapy has been used with some success for the treatment of painful gynecomastia.

Calcitoninemia

Calcitonin is a polypeptide hormone produced by the C cells of the thyroid. It diminishes the release of calcium from bone and increases the excretion of urine calcium, sodium, and phosphate. Interestingly, no clinical syndromes are associated with tumor production of calcitonin except for one reported case of a small cell carcinoma patient with hypercalcitoninemia and hypocalcemia (21). Calcitonin plays an important role as a tumor marker in monitoring patients with medullary carcinoma of the thyroid and in the diagnosis of multiple endocrine neoplasia type 2, a familial disorder characterized by medullary carcinoma of the thyroid, parathyroid adenomas, and pheochromocytoma. In addition to medullary thyroid carcinoma, a number of other cancers have been associated with elevations in calcitonin, including small cell (48–64%) and other lung cancers, carcinoid, breast cancer, colon cancer (24%), and gastric cancer (38%). With the exception of medullary thyroid carcinoma, the clinical usefulness of serum calcitonin levels as a tumor marker remains undetermined (22).

Acromegaly

Most cases of acromegaly result from growth hormone overproduction by pituitary tumors. Growth hormone elevations also may result from production of growth hormone releasing hormone by tumors, particularly pancreatic islet-cell tumors and bronchial carcinoids. Treatment of this paraneoplastic syndrome is directed at treatment of the underlying tumor. Occasionally, growth hormone releasing hormone secretion responds to administration of longacting somatostatin analogs (23).

Carcinoid Syndrome

The classic carcinoid syndrome is characterized by flushing, diarrhea, and bronchospasm. Less frequent signs and symptoms include coronary artery spasm leading to angina pectoris, pellagra, endocardial fibrosis, arthropathy, glucose intolerance, and hypotension. The symptoms are due primarily to the production of 5-hydroxytrytophan (serotonin), although secretion of other hormones, such as bradykinin, hydroxytryptophan, and prostaglandins, also may play a role. Carcinoid tumors are found throughout the gastrointestinal tract, including the esophagus, stomach, duodenum, jejunum, ileum, the Meckel diverticulum, appendix, colon, rectum, bile ducts, pancreas, and liver. They also have been found in the larynx, thymus, lung, breast, ovary, urethra, and testis.

The medical treatment of the carcinoid syndrome is directed at inhibiting serotonin synthesis and at blocking its effects peripherally. Different drugs can be used to accomplish these goals (24,25). Antiserotonin agents such as cyproheptadine hydrochloride and methysergide can ameliorate the diarrhea. For long-term treatment, cyproheptadine hydrochloride is the preferred medication because of the risk of retroperitoneal, cardiac, and pulmonary fibrosis associated with methysergide. Antidiarrheal agents such as loperamide hydrochloride and diphenoxylate hydrochloride also can be quite helpful in controlling the diarrhea.

Flushing appears to be due to the secretion of histamine. The administration of a combination of H_1 and H_2 histamine receptor antagonists often can control this symptom. Somatostatin analogs such as octreotide acetate are effective in controlling the symptoms of flushing and diarrhea in up to 75% of patients. Octreotide acetate is administered subcutaneously every 8 hours. Side effects include hypoglycemia, steatorrhea, and cholelithiasis. Carcinoid syndrome associated with bronchial carcinoid tumors has distinctive features and is treated differently. Many patients experience improvement in symptoms with glucocorticoids or phenothiazines.

Extrapancreatic Tumor Hypoglycemia

Tumors most likely to cause hypoglycemia are of mesodermal origin, such as fibrosarcomas and mesotheliomas, or of epithelial origin, such as hepatomas, adrenal cortical carcinomas, and gastrointestinal adenocarcinomas. Hypoglycemia usually occurs in the late stages of malignancy. The mechanism by which hypoglycemia occurs involves a combination of impaired hepatic glucose production and increased peripheral glucose utilization. Many patients have poor nutritional status, with depleted stores of the glycogen and protein needed to sustain hepatic glycogenolysis and gluconeogenesis. Hepatic damage from metastases further limits the ability to sustain gluconeogenesis. In most patients, however, hypoglycemia results predominantly from increased peripheral glucose utilization, raising the possibility of production of hormones with insulin-like properties. Insulin levels, as well as levels of insulin-like growth factor I and growth hormone, are low, whereas insulin-like growth factor II (IGF-II) levels are usually normal. Recent work has focused on tumor production of an abnormally processed variant of IGF-II, “big IGF-II.” This variant is not measured in usual radioimmunoassays for IGF-II but possesses normal biological activity. It is likely that “big IGF-II” accounts for many or most cases of tumor hypoglycemia (26,27).

Symptoms of hypoglycemia result from neuroglycopenia (confusion, seizures, and coma) or from activation of the adrenergic nervous system (sweating, palpitations, hunger, and tremors). The presence of tumor-associated hypoglycemia is established by demonstrating a low serum glucose level (less than 40–50 mg%) in a patient with symptoms of hypoglycemia who responds to oral or intravenous glucose. No further diagnostic workup is necessary. The primary treatment is nutritional support, either oral or intravenous. For immediate relief of symptomatic hypoglycemia, glucose is given as an intravenous bolus of 50% dextrose and then continued as a drip of

10% glucose. Refractory hypoglycemia can be treated with the counterregulatory hormones glucagon or cortisone.

ENDOCRINE DISEASES IN CANCER PATIENTS

Malignancies often occur in patients with preexisting medical conditions such as diabetes mellitus and thyroid disease. Treatment of these conditions must continue during and after treatment of the malignancy and during palliative care. In each condition, goals of treatment must be reevaluated with prognosis of the underlying malignancy in mind.

Diabetes Mellitus

Standard guidelines for the treatment of both type I and type II diabetes mellitus generally can be followed in the cancer patient; however, the appropriateness of “tight control” needs to be addressed in these patients. Based on results of the Diabetes Control and Complications Trial (28), it is accepted that intensive insulin treatment of type I diabetes results in a decrease in microvascular complications. These results have been extrapolated to type II diabetes mellitus (29); however, in the cancer patient with a limited life expectancy, intensive insulin therapy to prevent long-term complications is not a reasonable goal. The major complication of intensive insulin therapy is an increased risk of hypoglycemia. In patients with malignancies and poor nutrition, the risk of hypoglycemia is increased further. Additionally, intensive insulin treatment requires frequent blood sugar monitoring, which may place a further burden on the patient and his or her caregivers. Sulfonylurea agents frequently are included in treatment regimens for type II diabetes. In the cancer population with suboptimal nutrition, recent weight loss, or impaired kidney or liver function, these agents should be used with extreme caution. Severe prolonged hypoglycemia can result from using sulfonylurea drugs. Many type II diabetics previously treated with these agents can have their diabetic medication discontinued because of normalization of blood sugars secondary to weight loss and poor calorie intake.

Diets should be tailored to meet the needs of the individual patient. Patients with poor appetite and decreased oral intake should be allowed to liberalize their diets from the traditional “diabetic diet.” Patients may experience early satiety and mechanical problems with chewing and swallowing; nutritional supplementation with commercial products may be necessary. Consultation with a registered dietitian is helpful when devising an appropriate diet for the cancer patient with diabetics.

In summary, when choosing an appropriate treatment for diabetes mellitus in the cancer population, reasonable goals should be chosen. An attempt should be made to avoid symptomatic hyperglycemia, to decrease the risk of hypoglycemia, and to provide the patient with as many dietary choices as possible.

Euthyroid Sick Syndrome

Severe illness, whether acute or chronic, can cause changes in thyroid physiology, leading to what has been referred to as the *euthyroid sick syndrome* (30). Changes can occur in levels of total thyroxine (T_4) and, to a lesser extent, free thyroxine and TSH levels. T_4 is decreased due to its decreased binding to its serum transport proteins. The decrease in triiodothyronine (T_3) results from inhibition of 5'-deiodinase, the enzyme that converts T_4 to T_3. Low T_4 levels are associated with a higher mortality rate; TSH levels are generally helpful in distinguishing euthyroid sick syndrome from pituitary hypothyroidism. In addition, free thyroxine levels are usually normal.

Adrenal Insufficiency

Because of the vascular nature of the adrenal cortex, the adrenal glands are common sites of metastatic disease. Typically, adrenal metastases are found incidentally during abdominal computed tomography and magnetic resonance imaging scans and are usually of no functional significance. In a minority of cases, bilateral adrenal cortical destruction is sufficiently advanced to impair normal functioning and result in deficient production of cortisol (31). Symptoms of adrenocortical deficiency overlap with typical symptoms of advanced malignancy and include weight loss, fatigue, nausea, anorexia, and hypotension. The presence of hyponatremia or hyperkalemia further suggests the diagnosis.

The ACTH stimulation test is the most direct diagnostic study used to exclude adrenocortical insufficiency. A normal test contains the following three elements: a morning basal cortisol of at least 7–9 µg/dl, an increase greater than 7 µg/dl 30 minutes after administration of 0.25 mg intravenous ACTH, and a maximum response to intravenous ACTH of 18–20 µg/dl or greater.

Severely symptomatic adrenal insufficiency *(adrenal crisis*) is treated with intravenous saline and stress doses of hydrocortisone, 100 mg intravenously every 8 hours, tapered to a chronic oral maintenance dose of 20 mg every morning and 10 mg every evening. Patients with concomitant aldosterone deficiency resulting in hyperkalemia also may require the addition of the oral aldosterone analog fludrocortisone acetate (0.05–0.20 mg daily).

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36

HEADACHE AND OTHER NEUROLOGIC COMPLICATIONS

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Intracranial pathology can result in a variety of distressing symptoms. Fortunately, the underlying cause often can be identified and treated, and the accompanying symptoms commonly respond to supportive measures.

This chapter is divided into two sections. The first deals with headache and other symptoms of intracranial pathology and reviews their pathogenesis and management strategies. Although nausea and vomiting are common in patients with intracranial pathology, this topic is covered elsewhere in this volume. The second section reviews cancer-related neurologic syndromes, such as brain metastasis, base of skull metastasis, and cerebrovascular disease; oncologic interventions and supportive care strategies are outlined for each.

SYMPTOMS OF INTRACRANIAL PATHOLOGY

Headache

Assessment

Principles of headache assessment used for the general medical population (1) can be useful for patients with a cancer history, with one important exception: Headache in a cancer patient often heralds serious disease. The potential for headache to be the presenting symptom of a serious complication of the disease or its treatment compels an early and thorough assessment for structural disease. This assessment begins by confirming the onset, duration, progression, and focality of the headache. Pain characteristics include qualitative descriptors, severity, exacerbating and relieving features, associated symptoms, and the outcome of analgesic drugs or other therapies. Although prior headache history is important, the burden of proof is to rule out a new and serious cause of headache; brain metastasis can present with a headache similar to a previously experienced benign headache (2).

Cancer or its treatment can cause headache in a variety of ways. Some processes are considerably more likely to occur at particular points along the course of the disease. For example, approximately 90% of patients who die of melanoma have central nervous system metastases at autopsy; disseminated metastases are less likely to occur until regional metastases have developed. Therefore, the cancer history, extent of known disease, and prior treatments should be determined for all cancer patients with a headache.

The physical examination of the cancer patient with headache begins with a general physical examination and screening neurologic examination, including examination of the ocular fundi, range of motion of the cervical spine, and assessment for meningismus. Provocation of the pain by the examiner can be informative: An underlying pathological process is usually not far from the area of tenderness. Sites of pain indicated by the patient should be inspected and palpated. The examiner should palpate over facial sinuses, bony skull prominences, the occipitonuccal junction, and neck arteries. The orbits should be gently palpated and examined for proptosis. If the patient's pain is provoked by any of these maneuvers, the pain referral pattern should be noted.

Although comprehensive investigations can help document the cause of headaches caused by cancer, the extent of investigation should be guided according to the clinical situation. Bone scintigram, computed tomography (CT) of the head with fine bone windows, magnetic resonance imaging (MRI), and spinal fluid examinations are all commonly used in headache assessment. Blood tests can include serum hemoglobin, blood gas levels, and sedimentation rate.

Head pain usually originates from intracranial or extracranial pain sensitive structures. Nociceptive input from these sites arises by displacement, distention, or inflammation of vascular structures, by sustained contraction of muscles, or by direct pressure on nerves. Alternatively, head pain may arise from nonnociceptive mechanisms arising from damage to peripheral or central pain pathways that subserve the head.

Anatomy of Head Pain

Pain-sensitive structures in the head include the fifth, ninth, and tenth cranial nerves; the upper three cervical nerves; and the great venous sinuses and their tributaries from the surface of the brain. In addition, all the tissues covering the cranium, especially the arteries, are pain sensitive. The cranial bones, diploic and emissary veins, brain parenchyma, parts of the dura, most of the pia mater and arachnoid, and the ependymal lining of the ventricles and choroid plexus, are insensitive to pain.

Nociceptive input from supratentorial structures, including the superior surface of the tentorium cerebelli, causes pain to be felt anterior to a line drawn from the ears across the top of the head. Damage to these structures activates branches of the trigeminal nerve. Nociceptive input from infratentorial structures, including the inferior surface of the tentorium cerebelli, causes pain to be experienced posterior to this line and is conveyed by sensory fibers in the fifth, seventh, ninth, and tenth cranial nerves and the upper three cervical nerves (3).

Primary and Secondary Headaches

Primary headaches, migraines, tension-type headaches, cluster headaches, and others are the most frequent headache types in Western society. They are functional disorders that, by definition, are characterized by the absence of a structural lesion. In contrast, secondary headaches are symptomatic of an underlying disease, either an intracranial lesion or systemic process. The International Headache Society has provided a comprehensive classification of headache that identifies eight groups of secondary headaches (4) (Table 36-1). Although a temporal relationship between the headache and the underlying disorder is usually apparent, the diagnosis can be challenging because of the high prevalence and similar features of primary headaches.

Head trauma
Vascular disorders
Nonvascular intracranial disorder
Substances or their withdrawal
Noncephalic infection
Metabolic disorder
Disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial structures, cranial neuralgias, nerve trunk pain, and deafferentation pain
Headache not classifiable

Modified after Olesen J. Headache classification committee of the International Headache Society: classification and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain. Cephalalgia 1988;7[Suppl 8]:1, with permission.

TABLE 36-1. SECONDARY CAUSES OF HEADACHE

The incidence of headache in patients with primary or metastatic brain tumors is approximately 50% (5). Headache is a presenting symptom in 30–60% of adult brain tumor patients, and 60–70% of patients develop headache during the course of this illness (6,7). Primary and metastatic brain tumors have a similar incidence of headache in a New York– based study (8), although other studies report higher headache occurrence in primary than metastatic tumors (7,9). The median duration of headache at diagnosis, ranging from 3.5 weeks in the New York study (8) to 15.7 months in a study from Bangkok (7), may depend on socioeconomic factors, such as access to neurosurgical expertise and neuroimaging.

Factors reported to influence the incidence of headache in patients with brain tumors include tumor location, rate of growth, increased intracranial pressure (ICP), size of the enhancing lesion, amount of midline shift, and a history of previous headache (2). Headache occurs more commonly in infratentorial (64–84%) than supratentorial (34–60%) tumors (5,6 and 7,10,11) and is especially common with midline and basal tumors (95% and 70%, respectively). Slowly growing tumors such as low-grade supratentorial astrocytomas and neuroepithelial tumors (including gangliogliomas, dysembryoplastic neuroepithelial tumors, and pleomorphic xanthoastrocytomas) have a low headache incidence but frequently are associated with seizures (12,13,14 and 15). Faster growing tumors, particularly high-grade gliomas, have been reported to cause headache in approximately one-half of patients but have a lower incidence of seizures.

The classic brain tumor headache is characterized by its progressively increasing severity, frequency, and duration; early morning awakening; disappearance after rising; association with nausea and vomiting; and aggravation by the Valsalva maneuver. This syndrome is actually uncommon, occurring in only 17–28% of patients (5,16). In reality, no single headache pattern is typical of a brain tumor. The most common headache profile is bifrontal, often worse ipsilaterally, dull, nonthrobbing, and aching in nature. These characteristics are similar to a tension-type headache. The pain is usually mild to moderate, intermittent, and relieved by simple analgesics in approximately one-half of patients. Severe headaches are reported by approximately 40% of patients, and 45% indicate that headache is the worst symptom. Also, 30–70% of patients experience nocturnal headache, and only 18–36% report early morning headache. Positional changes, either supine to standing or standing to supine, induce or aggravate headache in 20–32%; in 18–23% of patients, the headache worsens with Valsalva maneuvers. Nausea and vomiting are associated with headache in 36–48% of patients (5,6 and 7,17).

Brain tumor headaches may mimic primary headaches. Forsyth and Posner (2) found that tumor headaches were similar to tension-type headaches in 77% of patients; 9% had migrainelike headaches, and 14% had other types. In one study of cancer patients with a significant history of prior headache, 78% experienced new headaches associated with their brain tumor (5). The brain-tumor headache may be similar to the patient's prior headache but is generally more severe, frequent, or associated with new symptoms or abnormal signs.

The location of the headache in relation to tumor site, the presence of raised ICP, and the localizing value of focal headache depend on the mechanism by which headache is produced. Two mechanisms commonly account for headache in brain tumor patients: (a) direct traction or distortion of painsensitive structures by the tumor mass, and (b) distant traction through extensive displacement of brain tissue, either directly by the mass (e.g., herniation syndromes) or by hydrocephalus caused by obstruction of cerebrospinal fluid (CSF) pathways (17). Direct traction accounts for the localizing value of headaches in patients without raised ICP. Supratentorial tumors not associated with raised ICP often produce bilateral headache in the frontal region (85%). Unilateral headache is present in 28–53% (5,7), and the headache usually lateralizes to the side of the tumor. With the exception of cerebellopontine-angle tumors, which are more likely to produce symptoms by compression of adjacent cranial nerves, posterior fossa tumors often present with posterior head pain as the first symptom.

The headache of increased ICP tends to be severe, aching, and constant; is unrelieved by simple analgesics; is worse in the morning and with Valsalva maneuvers; and is associated with nausea or vomiting. It is most commonly located in the frontal region, either bifrontal or vertex, or in the neck alone. Occasionally, increased ICP accounts for the surprising occurrence of occipital headaches in association with a supratentorial tumor or frontal headache in association with a posterior fossa tumor.

Increased ICP is not necessary for the occurrence of headache, nor is it always associated with headache. Headache is commonly associated with “plateau waves,” however, which may occur when increased ICP is severe. Plateau waves are transient elevations in ICP, which range from 25–60 mm Hg and last 1–10 minutes (18). They may be either spontaneous or induced by Valsalva maneuvers or changes in body position. In addition to headache, these episodes may be associated with impaired hearing or vision, nausea, vomiting, photophobia, lethargy, and transient neurologic deficits. Severely increased ICP ultimately can result in life-threatening cerebral herniation syndromes and sudden death.

Intracranial Pathology: Analgesic Strategies

Management strategies for patients with pain from intracranial pathology derive from the general principles of supportive care and focus on both oncologic interventions and analgesic interventions (Table 36-2). The use of surgery to manage symptoms from intracranial pathology is limited to highly selected patients who may be offered procedures to relieve specific syndromes that are refractory to more conservative treatment. For example, rare patients undergo resection of a large cerebellar metastasis to reduce severe headache, despite the presence of other, less symptomatic metastatic lesions. Others are offered percutaneous aspiration of a tumor cyst through an Ommaya reservoir, if relief of mass effect on initial aspiration results in significant relief of symptoms (19).

Oncologic interventions
Radiation therapy
Surgery
Chemotherapy
Analgesic interventions
Pharmacotherapy
Physical measures
Psychological measures
Neurolytic or anesthetic procedures
Neurostimulatory procedures

TABLE 36-2. MANAGEMENT STRATEGIES FOR PAIN FROM INTRACRANIAL PATHOLOGY

Radiotherapy is frequently effective to relieve pain or other symptoms from metastatic disease, even if the primary tumor is relatively radiation resistant (20,21 and 22). If the goal of treatment is limited to symptom control alone, patients are generally candidates for radiotherapy if life expectancy is greater than 2 months and symptoms are not easily managed with more conservative means.

Chemotherapy can be palliative for metastatic intracranial disease from specific tumor primaries, including breast (23), small cell carcinoma of the lung (24), testes (25), and others. Hormonal therapy can be well tolerated and can be effective to shrink metastatic disease in patients with breast or prostate cancer who have not previously been exposed to such treatment.

The role of corticosteroids to manage symptoms from intracranial pathology requires particular emphasis. An empiric course over a few days can be used to establish efficacy (26). Although dexamethasone is usually preferred, prednisone (27), prednisolone (28), and adrenocorticotropic hormone (29) also have been reported to relieve symptoms from intracranial pathology. Dexamethasone is available in both oral and parenteral formulations, and generally lacks mineralocorticoid effect. Nonfluorinated corticosteroids such as prednisone may have less risk of causing myopathy (27,28). Controlled trials comparing the efficacy and side effect profile of different steroids are needed. The dose–effect relationship of dexamethasone is also a controversial subject, and the optimum dose for tumor-related cerebral edema has not been established. Comparison of 4-, 8- and 16-mg/day dexamethasone (Decadron) therapy in 89 patients with CT-proven brain metastasis, no signs of impending herniation, and Karnofsky scores of 80 or less showed the same degree of improvement in Karnofsky score over 1 week, and more frequent toxicity in the 16-mg/day group over 4 weeks (30). Another study of 12 patients with brain metastasis treated with high-dose dexamethasone for 48 hours reported complete responses in only three patients, partial response in one, and no response in eight (31). Other reports support using steroid doses much higher than the conventional 4 mg every 6 hours, up to 96 mg over 24 hours, suggesting that the ideal dexamethasone dose should be established for each individual patient (32,33).

In brain tumor patients, cushingoid facies predict the presence of steroid myopathy (27). Other side effects of steroids include hyperglycemia, cataracts, osteoporosis, and neuropsychiatric effects. Side effects can become disabling over time. To reduce the risk of side effects, the lowest effective dose of steroid should be identified by methodical titration upward or downward.

Neuropathic Pain Due to Central Nervous System Disease

Central pain is defined as pain associated with a lesion of the central nervous system, particularly of the spinothalamic tract or thalamus (34). Central pain must be differentiated from other types of neuropathic pain associated with lesions of the peripheral nervous system and from nociceptive pain associated with ongoing stimulation of nociceptors by a tissue-damaging lesion. Current theories of central pain postulate selective deafferentation of the spinothalamic tract over prior concepts of thalamic pain as the more likely underlying mechanism (35).

Many types of structural lesions in the brain and spinal cord can cause central pain. Although the type, duration, and size of the lesion can influence the tendency to produce central pain, similar lesions may or may not be painful, or they may produce different types of pain (36). Only a minority of patients with susceptible lesions actually develop central pain. The locations of most painful lesions are in the spinal cord, lower brainstem, and ventral posterior part of the thalamus (37,38 and 39). The most common causes of these lesions are spinal cord trauma and cerebrovascular accidents. The prevalence of central pain is highest in syringomyelia; most patients with this lesion develop central pain during the course of the disease. Central pain is less common in traumatic spinal cord injuries (30%) and multiple sclerosis (23%). Interestingly, intracranial and spinal tumors have a low prevalence of central pain. Several patients with central pain due to meningioma have been reported (40). In a series of 49 patients with thalamic tumors, only one had central pain (41).

The diagnosis of central pain depends on a detailed neurologic history and examination along with laboratory investigations, including CT or MRI scans, CSF analysis, neurophysiologic testing, and other tests as appropriate. Symptoms characteristic of central pain are rarely psychogenic in origin (36).

The onset of central pain may be immediate or delayed, first appearing years after the original problem. Although the pain typically has a burning, tingling, or “pins and needles” quality, it may be superficial, deep, or both. It is not always dysesthetic, and can have a variety of descriptors in the same or different regions. The sensation is often unlike any prior experience and is typically difficult to describe (35). The pain may be triggered by physical activity, stress, loud noise, vibrations, weather changes, altered muscle or visceral function, or seizures (37). It is usually constant, varies in severity from mild tingling to unbearable, and may have more than one element; commonly, a severe intermittent component is superimposed on constant pain. Central pain is usually permanent, although transient pain in spinal cord injury patients and complete cessation of pain either spontaneously or after the occurrence of new lesions have been reported (36,42,43). Although not necessary for its development, central pain usually is associated with a sensory deficit in the same area as the pain. Hypesthesia to temperature is the most common finding. Sensory deficits are consistent with the site of the known lesion; for example, ventral posterior thalamic lesions may be associated with a hemibody sensory loss, and low brainstem infarcts may produce a crossed, dissociated sensory loss.

The management of central pain is based largely on clinical experience. Treatment modalities include pharmacotherapy, sensory stimulation, neurosurgical procedures, and sympathetic blockade (37,44). The first-line drugs are antidepressants with noradrenergic properties, specifically amitriptyline hydrochloride, which appears to be the most effective but also has the most side effects. Other medications have been found to be effective in randomized, controlled trials for central pain, including intravenous lidocaine (45) and oral lamotrigine (46). Second-line drugs include antiepileptics (AEDs) and membrane-stabilizing drugs, the most effective being carbamazepine. Other newer AEDs of potential benefit, such as gabapentin, have not yet been subjected to double-blind clinical trials (35). The best central pain response to antidepressants is seen in poststroke patients, whereas AEDs seem to be most effective for paroxysmal central pain, especially in multiple sclerosis (36). Nonsteroidal anti-inflammatory drugs and opioids generally have a weak or no effect. A range of other therapies are used, including g-aminobutyric acid (A) agonists (e.g., diazepam [Valium]), intrathecal baclofen, clonidine, neuroleptics, systemically administered local anesthetics, and naloxone hydrochloride (47). Stimulation techniques include low- and high-frequency transcutaneous electrical nerve stimulation, spinal cord stimulation, and deep brain stimulation. Motor-cortex stimulation, a relatively new technique, is reported to benefit certain forms of intractable pain (48).

Cranial Neuralgias

Cranial neuralgias are of particular significance to the cancer patient, as they frequently lead to a diagnosis of base of skull or neck metastases. Also, the frequent response of these pain syndromes to a regimen containing selected adjuvant analgesics (e.g., anticonvulsants) highlights the value of prompt diagnosis. Trigeminal neuralgia and glossopharyngeal neuralgia are characterized by paroxysmal lancinating pain in the face or throat and neck, respectively. Pain lasts from a few seconds to a minute or two, with frequent recurrence. The pain is often spontaneous in onset, but it may be initiated by sensory stimuli such as touch or tickle applied to certain trigger areas; movements such as chewing or talking also can precipitate pains. Other features, such as continuous dull aching, burning, or pressure pain, are often reported (49). The differential diagnosis includes disorders of the jaw, teeth, sinuses, base of skull, and neck. Although these neuralgias are most commonly idiopathic, the onset of cranial neuralgia in a patient with a cancer history mandates a search for metastatic disease. Numb chin syndrome, involving facial and oral numbness in the distribution of the mental nerve, has been associated with a metastatic etiology in 89% of patients (50). Radiological studies include CT or MRI with views of the base of skull and sinuses. Plain radiographs or tomograms of the skull base may show abnormalities. CSF analysis may be abnormal in patients with associated leptomeningeal metastases.

Seizures

A seizure may be defined as an episode of uncontrolled motor, sensory, or psychological activity caused by the sudden excessive discharge of cerebral cortical neurons (51,52), followed by a postictal phase of metabolic cerebral depression lasting a variable period. There are two broad types: primary generalized seizures and partial (also called focal or secondary) seizures. A partial seizure is caused by an epileptogenic lesion. Clinically, a seizure discharge is most effectively identified by electroencephalography, whereas an epileptogenic lesion may be demonstrated by CT or MRI scanning. The first appearance of any seizure during adulthood, with or without a localizing aura, is sufficiently suspicious to warrant an investigation for neoplasm.

Generalized or focal seizures occur in 20–50% of patients with brain tumors (52). The occurrence of a seizure depends on tumor site, type, and infiltration or expansive properties. In patients with supratentorial tumors, seizures are a presenting symptom in up to half of patients (53,54). The highest seizure incidences occur with oligodenrogliomas (92%), astrocytomas (70%), meningiomas (67%), and glioblastomas (37%) (56). In patients with slow-growing chronic tumors, the seizure incidence is as high as 75% and may predate other symptoms for years (56). The time interval from first seizure to tumor diagnosis was 16 months in one European study (61). Focal seizures are associated with tumors involving motor cortex, sensory cortex, or the temporal lobe. Temporal lobe gliomas typically produce psychomotor seizures, with or without olfactory hallucinations (uncinate fits); abnormal visual or auditory perception; déjá vu phenomenon; or automatic behavior (57). Parietal lobe tumors may cause generalized or focal sensory seizures, and occipital lobe neoplasms have been associated with an aura of flashing lights, but not formed images. Infratentorial tumors and neoplasms involving the white matter only are not commonly associated with seizures.

In patients with intracerebral metastases, the incidence of seizures as a presenting symptom ranges from 15% to 21% (16,58,59). Thirty percent to 40% of patients experience at least one seizure (60). In one study, late seizures developed in 10% of patients from 1 to 59 weeks after diagnosis of intracerebral metastases (60). With the exception of malignant melanoma and choriocarcinoma, metastatic brain neoplasms are less likely to cause seizures than primary brain tumors. The presence of multiple metastases or combined brain and leptomeningeal metastases are the conditions most frequently associated with seizures (62). Seizures associated with cerebral metastases are usually of the simple or complex partial type (62).

Seizures can be an indication of tumor progression or recurrence, often occurring late after initial oncologic therapy. Other etiologies, such as electrolyte disturbances (e.g., hyponatremia), drug interactions, and noncompliance with anticonvulsants may predispose to the late development of seizures. *Status epilepticus*, defined as a persistent seizure (usually considered to last longer than 5 minutes) or repeated seizures without interictal return of consciousness, is an important neurooncological emergency. All clinicians should be familiar with the treatment of this condition. Acute management begins with assurance of the airway, ventilation, and perfusion. Blood should be sampled for urgent electrolyte screen and other appropriate tests, and a dose of glucose should be given (usually 50 ml of a 50% solution) before any results are known. The typical treatment protocol involves the intravenous administration of a benzodiazepine, such as lorazepam or diazepam, followed by intravenous loading with phenytoin or valproate sodium. Persistent seizure activity beyond 7–10 minutes is an indication for continuous electroencephalography monitoring and to start general anesthetic procedures, with intubation followed by a short-acting barbiturate (pentobarbital sodium or thiopental sodium), midazolam hydrochloride, or propofol (63). The minimal dose of anesthetic agents required to stop electrographic seizures is generally recommended. Although focal continuous epilepsy (epilepsy partialis continua) is also treated promptly, this syndrome is less injurious to the patient and usually is treated without the high-dose intravenous drugs administered for generalized status (64).

The routine use of prophylactic anticonvulsants in brain tumor patients is recommended in patients who present with seizures and in patients undergoing craniotomy. There are, however, no published data showing efficacy of anticonvulsants in preventing further seizures (65). The most commonly prescribed drug is phenytoin, in doses of 300–400 mg/day. Carbamazepine, phenobarbital, and valproate sodium also are used. Patients with benign brain tumors and no history of seizures do not require prophylaxis.

There is currently conflicting advice regarding the use of prophylactic anticonvulsants in patients with malignant primary or metastatic brain tumors who have never had a seizure. In one study, a 10% incidence of late seizures in patients with brain metastases was noted regardless of whether prophylactic phenytoin was given (60); however, serum anticonvulsant levels were subtherapeutic in twothirds of the patients who developed seizures, which may explain the therapeutic failure. Two randomized prospective studies with over 130 patients have found no significant benefit of prophylactic anticonvulsants in preventing late seizures over placebo or no treatment in brain tumor patients who had no prior history of seizures (66,67). Therefore, routine use of prophylactic anticonvulsants is not currently supported by the literature although it continues to be practiced. Patients with cerebral metastases from melanoma should probably receive prophylactic anticonvulsants due to the higher risk of seizures (up to 50%) in this patient group (68).

Therapeutic anticonvulsant levels can be difficult to achieve in brain tumor patients, especially with concomitant use of dexamethasone, which increases the required dose of phenytoin (69). Interaction between phenytoin and dexamethasone also reduces the bioavailability of the dexamethasone (70). Toxic phenytoin levels may occur with frequent dosage adjustments and can produce side effects of nystagmus and ataxia, which can suggest tumor recurrence. Other potential complications from phenytoin include erythema multiforme and Stevens-Johnson syndrome, which have been associated with the combined administration of whole brain radiation therapy (WBRT) and phenytoin (71); myopathy (72); immunosuppressive effects specifically targeted against cell-mediated immunity (73,74); hepatoxicity; hyperkinetic movement disorder; and osteomalacia (75).

Discontinuation of seizure prophylaxis in patients with a benign tumor and preoperative seizures has been recommended only for patients with complete excision of a benign tumor who remain seizure free after 12 months. The risk of relapse remains at least 35% if the patient has had previous seizures (76).

Singultus (Hiccups)

Singultus (hiccups) is a forceful involuntary inspiration caused by spasmodic contraction of the diaphragm that terminates with sudden closure of the glottis. Closure of the glottis results in the characteristic hiccup sound. Hiccups serve no known physiological function (77) and are usually a transient benign disorder that resolves without medical therapy. Chronic hiccups may reflect underlying pathology, including a lesion that irritates the peripheral vagus or phrenic nerves, drug toxicity, metabolic abnormalities, infection, and intracranial disease. Rarely, chronic hiccups are psychogenic.

The mechanism of hiccup may involve dysfunction of peripheral components or central connections of the reflex arc. The afferent neural pathway is composed of sensory branches of the phrenic and vagus nerves as well as dorsal sympathetic afferents from T6 through T12. The principal efferent limb, which produces the diaphragmatic contraction, includes motor fibers of the phrenic nerve and efferent branches to the glottis and external intercostal muscles (inspiratory). There is reciprocal inhibition of the expiratory intercostal muscles. The separate innervation of right and left hemidiaphragms and the long course of the two phrenic nerves, each of which contacts various organs, account for the large variety of reported mechanisms for hiccup. Hiccups may be bilateral or unilateral; most occur in the left diaphragm. The central control of hiccups, although not yet fully defined, is believed to include a supraspinal center that is integrated with the respiratory center output to respiratory motor neurons in the spinal cord (78). Experimental electrical stimulation of the medulla in cats has demonstrated generation of hiccup-like responses in the medullary reticular formation lateral to the nucleus ambiguus, just rostral to the obex (79,80). Cells in the nucleus raphe magnus containing the inhibitory neurotransmitter g-aminobutyric acid may be the source of inhibitory inputs to the hiccups reflex arc. The reported rate of repetitive hiccups is between 4 and 60 per minute; the most common rate is 17–20 per minute— not surprisingly, similar to the respiratory rate (81).

Central nervous system causes of hiccups include parenchymal lesions within the medulla and local pathology causing medullary compression. Both of these lesions can produce dysfunction at the level of the vagal nucleus and the nucleus tractus solitarius (82). It also has been suggested that central nervous system conditions causing hiccups may release the normal inhibitory tone on the hiccup reflex arc (77). Specific lesions of the medulla include neoplasms, syringomyelia, infarction (often the territory of the posterior inferior cerebellar artery), and infections, including meningitis, encephalitis, neurosyphilis, and human immunodeficiency virus encephalopathy. Compressive lesions causing hiccups include neoplasms, hematomas, cavernomas, and bleeding into the fourth ventricle (83). Most lesions develop slowly, are located near the dorsolateral aspect of the medulla, and extend towards the obex (84).

Identification of serious underlying causes of hiccups depends on their duration, severity, and associated conditions. Benign hiccup bouts may last up to 48 hours and usually are related to gastric distension, alcohol ingestion, or emotional factors. Persistent hiccups are defined as a hiccup episode lasting longer than 48 hours but less than 1 month, and intractable hiccups are defined as a hiccup episode persisting longer than a month. Both are assumed to have an organic etiology until proven otherwise by extensive medical and laboratory investigations (85).

Neurogenic hiccups may require urgent management. Some patients experience severe fatigue as a result of sleep deprivation. Others develop respiratory irregularity or even respiratory arrest, probably related to a lesion at the medullary respiratory control centers (86). When respiratory difficulties occur, associated brainstem symptoms or signs are usually present. It should be noted that, with the exception of intubated patients or those with a tracheotomy, hiccups alone do not produce any significant ventilatory effect because the glottis closes almost immediately after the onset of diaphragmatic contraction (78).

The management of hiccups includes physical, pharmacological, and surgical interventions. Initial therapy should focus on elimination or treatment of the underlying cause. Physical stimulation of afferent nerve endings or certain end-organs may interrupt the hiccup reflex arc (87) and are the basis of anecdotal folk remedies, such as swallowing granulated sugar, breathing into a bag, and breath-holding. Physiologically, the hiccup reflex is inhibited by high arterial carbon dioxide tension (88).

Pharmacological measures for hiccups are supported by anecdotal experience. Numerous classes of drugs have been used, including antipsychotics, tricyclic antidepressants, anticonvulsants, antiarrhythmics, central nervous system stimulants, muscle relaxants, inhalation agents, local anesthetics, and gastric motility agents. The most commonly used and most consistently effective agent is chlorpromazine, a centrally acting major tranquilizer and dopamine antagonist. It is especially effective given as an intravenous bolus (89). The second drug of choice is metoclopramide, a gastric motility agent and dopamine antagonist (91,92 and 93). Other valuable agents include the anticonvulsants carbamazepine, phenytoin, and valproic acid and the antispasmodic baclofen. Surgical interventions are reserved for intractable hiccups that fail to respond to physical or pharmacological therapy. Phrenic nerve transection, crushing, or anesthetic blockade may be complicated by severe respiratory impairment, especially if both phrenic nerves are disrupted. In addition, such a procedure may fail to relieve hiccups (89). Phrenic nerve surgery is therefore a last resort and should be preceded by a local anesthetic block to assess efficacy and the potential respiratory compromise from diaphragmatic paralysis (93).

Neurologic Impairments Caused by Intracranial Pathology

Focal neurologic symptoms such as weakness, numbness, incoordination, and visual impairment can interfere significantly with function. If correctly diagnosed, treatment of the underlying cause may be possible. In all cases, measures to accommodate the deficit can be helpful. Although the spectrum of manifestations resulting from intracranial disease are protean, two complex neurologic syndromes and specific neuropsychiatric conditions deserve emphasis because of the high degree of impairment and the clinical difficulty in making a correct diagnosis.

Patients with bifrontal disease may appear to the family as lacking initiative and sparkle. Speech is sparse or nonexistent (*mutism*), and yet the patient is fully aware of the conversation around him or her. There may be urinary urgency or incontinence (“unwitting wetting”); a shuffling, wide-based gait; and an apparent slowness of thought processes. Damage to both frontal lobes can be a sequela of radiation therapy or can result from multiple bilateral metastases, hydrocephalus, leptomeningeal tumor, cerebrovascular disease, or other causes. Findings on examination that support the diagnosis include bilateral grasp reflexes, a snout reflex, a positive glabellar tap, presence of bilateral palmomental reflexes, and an apraxic gait. Families need to be aware that the patient may be cognitively intact and able to later recall details of events that occurred while he or she was sick. Understanding that the lack of motivation is neurologic, rather than psychological, may help the family cope with the patient's condition.

In the nondominant parietal syndrome, there is denial of illness and the patient may believe he or she should be able to manage alone at home despite severe impairment. Brain metastases and cerebrovascular disease are the most common causes. The diagnosis of a nondominant parietal syndrome is confirmed by identifying focal sensory or motor deficits (usually affecting the left side of the body), hemianopsia, dressing and constructional apraxia, agnosia, and denial of body parts (neglect). The overall management and rehabilitation strategies are similar to those used for other neuropsychological impairments. The prognosis for improvement is poor as a result of the patient's lack of insight.

Intracranial pathology also can cause delirium and specific disorders of mood or perception. Delirium is an acute organic disorder of attention and cognition. Thinking, perception, memory, and psychomotor status all may be disturbed in the delirious patient (94). In contrast to dementia, delirium is acute and potentially reversible. Delirium involves a wide differential diagnosis in which toxic and metabolic disorders are prominent. In addition to neoplasm, many other structural disorders may be responsible, including hydrocephalus, stroke, subdural hematoma, cranial arteritis, and trauma (95). Delirium also may be caused by seizures. New onset of delirium requires prompt assessment for treatable causes.

Personality changes, including depression, euphoria, loss of inhibition, and impulsive behavior, also may reflect intracranial disease, including raised ICP secondary to a space-occupying lesion. Temporal lobe lesions have been noted to produce bizarre thinking and immature emotional behavior (57). The diagnosis of these

conditions, particularly the organic mood disorders, may be challenging given the high prevalence of primary psychiatric disorders in the cancer population.

CANCER-RELATED NEUROLOGIC SYNDROMES

Brain Metastases

Clinically evident brain metastases occur in 20–30% of patients with systemic cancer and are found at autopsy in up to 50% (20,96,97,98,99 and 100). Metastases are the most common malignant tumor of the brain (97) and have an annual incidence three times that of primary brain tumors (98,99). The three most common cancers that metastasize to the brain are lung, breast, and melanoma (97).

Brain metastases tend to be a late finding; evidence of other metastatic disease is usually present. Only 19% of 201 patients with brain metastases studied at the Memorial Sloan-Kettering Cancer Center lacked evidence of systemic metastases on initial evaluation (20). The interval between diagnosis of the primary malignancy and the discovery of brain metastases depends on the tumor type. Small cell lung cancer, for example, metastasizes early; there is an 11% incidence of silent metastases at diagnosis (101). Other tumors, such as breast carcinoma, typically develop brain metastases late, once disseminated disease is present (102,103 and 104). In addition to the primary cancer, factors that influence brain metastases include age and gender (105). Some tumors, such as breast or renal cancers, tend to cause single lesions, whereas others, such as melanoma, lung cancer, and tumors of unknown origin, are more likely to cause multiple metastases (106). In lung cancer and melanoma patients, men have a greater predilection to develop brain metastases than women, perhaps reflecting the more common site of melanoma in men on the head, neck, and trunk; for lung cancer, explanations for this observation are lacking (105). Certain metastatic brain tumors are prone to hemorrhage, melanoma, choriocarcinoma, renal cell carcinoma, and bronchogenic carcinoma (107). Skull metastases occur with cancers of the breast and prostate (106).

The distribution of brain metastases is proportional to cerebral blood flow as well as brain weight (110). The cerebral hemispheres receive 85% of cerebral blood flow and are the site of approximately 80% of brain metastases. The posterior fossa, the recipient of 15% of cerebral flow, is the site in 20% of metastases (16% are in the cerebellum and 3% are in the brainstem) (105,111). The observation that there is a predilection of gastrointestinal and pelvic malignancies to metastasize to the posterior fossa suggests a route of dissemination via Batson's plexus, which may receive venous drainage from the pelvic organs, but the evidence for this is not conclusive (103,108,112).

The location of brain metastases is frequently at the gray–white matter interface, or at vascular borders called “watershed zones”; the latter account for one-third of the total brain volume, but two-thirds of brain metastases (113). In these regions, the blood vessels rapidly branch into end capillaries and may act as a trap for metastatic cell emboli (114).

The most common presenting symptoms are headache, weakness, and behavioral changes (116). Patients usually have focal findings, which typically exhibit an onset over days to weeks and have a progressive course. Although focal signs often suggest the site of metastases, false localizing signs may occur as a result of compression of distant structures by shifts caused by increased ICP. These signs may cause a perplexing constellation of symptoms and signs. Generalized neurologic dysfunction caused by raised ICP may present in an acute or gradual manner.

Headache is the most common initial complaint. It occurs in half of patients with a single brain metastasis, and almost all these patients manifest other signs or symptoms. Patients with multiple or cerebellar metastases have a higher incidence of headache (105,106). Papilledema occurs in less than one-fourth of patients with brain metastases (109,112). Focal weakness, the second most common presenting symptom, is reported in approximately 40% of patients, although examination reveals weakness in up to two-thirds of patients (111,120). Mental or behavioral changes, an initial finding in 30% of patients, may reflect multiple brain metastases or focal lesions causing raised ICP or hydrocephalus. One study reported that three-fourths of brain metastasis patients failed to score normally on standard mental status tests (121). Seizures, either focal or generalized, are the first sign in 15–20% of patients. Occasionally, transient neurologic events occur with complete resolution; excluding seizures, an acute onset of symptoms has been reported in less than 10% of patients. The complaint of gait ataxia can result from posterior fossa, a large frontal lobe lesion, or hydrocephalus. These patients may lack significant unsteadiness on examination. Other presenting symptoms include sensory disturbance and vision loss, typically hemianopsia. The onset of neurologic dysfunction may be insidious, over weeks or months. Intratumoral hemorrhage may cause an acute worsening of preexisting, slowly evolving symptoms.

The most sensitive diagnostic test for brain metastases is MRI. This test should be considered for any cancer patient with an unexplained neurologic disturbance. It also is indicated for neurologically asymptomatic patients undergoing attempted curative treatment of a primary tumor with high metastatic potential to brain, such as lung cancer or metastatic melanoma (117). Gadolinium-enhanced MRI reveals multiple metastases in approximately 70% of patients, compared to 50% with CT (118). Features that suggest a metastatic lesion include round appearance with “ring” enhancement, location at the gray–white matter junction, and vasogenic edema (119).

Evaluation of the status of the systemic cancer is important in determining appropriate therapy for an intracranial metastasis. Factors that affect the choice of treatment modality for brain metastases include patient age, size and location of the metastasis, neurologic status, patient performance status, extent of the primary tumor, other sites of metastatic disease, and response to prior therapy (105,115). Therapeutic options range from no treatment, which may be appropriate in patients near death with disseminated disease, to emergency surgery for potentially reversible but otherwise imminently fatal lesions. Most commonly, various combinations of medical, radiation, and surgical therapy are employed.

Without treatment, patients with brain metastases have a median survival of approximately 1 month (122,123). Corticosteroids double the median survival to 2 months (124,125). Approximately 70% of patients show significant improvement by day 2 of treatment (126). To reduce the risk of side effects, steroid dose is tapered downward from the starting dose, as tolerated.

WBRT is reported to increase median survival to 3–6 months (121,128,129). For patients irradiated, the death rate from neurologic progression of metastases is similar to that of systemic disease (127). Two-thirds of patients with serious neurologic dysfunction and one-third of patients with moderate dysfunction obtain relief or improvement of symptoms (105,130). The standard dose is 3000 cGy in 10 fractions (300 cGy per treatment), although regimens vary depending on the center. Protracted radiation therapy regimens (2000 cGy in 20 fractions) are advised when anticipated survival is greater than 1 year due to a lesser rate of later neurologic complications associated with this regimen (131). Accelerated radiation therapy may be used to achieve rapid palliation in patients whose condition is deteriorating quickly. Prophylactic cranial irradiation is advocated for newly diagnosed cancer patients with a high risk of developing brain metastases (e.g., small cell lung cancer) (114). This approach remains controversial despite significant reduction in cranial metastatic disease, as no consistent survival benefit has been shown (132). Other irradiation modalities include interstitial brachytherapy and radiosurgery (133).

Radiosurgery, which delivers a very high dose of radiation to a small target, has undergone an exponential growth in use and may eventually replace surgery as the primary treatment modality for small brain metastases not producing life-threatening mass effect. One series reported approximately 88% local control with a single fraction of 1600–3500 cGy (almost double the local control rate achieved with standard whole brain radiation) (133). Several reviews of this modality demonstrate comparable survival and local control to combined surgical resection and whole brain irradiation (114). It should be mentioned that whole brain irradiation is often given with radiosurgery to prevent more distant recurrence. One multicenter analysis by Auchter et al. (134) demonstrated a survival and functional independence advantage over surgical resection plus WBRT with a decrease in deaths from central nervous system progression. A prospective randomized trial is currently under way to compare whole brain irradiation with and without stereotactic radiosurgery. Factors influencing the efficacy of radiosurgery include size and shape of the lesion, number of tumors, and nature of the primary tumor. In general, welldemarcated, spherical tumors of small volume (<4 cm), without invasion deep into brain tissue, respond best to radiosurgery. The risk for distant recurrences increases significantly when more than three metastases are treated in one patient. Radiosurgery treatment for metastases secondary to melanoma and renal cell carcinoma has been associated with high quality of life even in the presence of multiple metastases, compared with lung cancer patients, who have a significantly shorter life expectancy. Relative contraindications to stereotactic radiosurgery include large tumors, hemorrhagic tumors, and tumors producing significant mass effect. Conventional treatment with surgery followed by WBRT is then recommended.

Of patients who exhibit an initial clinical response to radiotherapy, approximately 80% maintain clinical improvement at 3 months and 60% are stable at 6 months (104). Two-thirds of patients who show a major response to radiotherapy die of systemic disease, and only 15% die solely as a result of neurologic deterioration (117). Extent of systemic cancer is, therefore, a strong prognostic indicator in patients with brain metastases. The presence of liver or lung metastases predicts poor survival in patients who develop brain metastases.

Surgical interventions in patients with brain metastases encompass procedures to relieve ICP, biopsy to establish diagnosis (principally in patients with an unknown primary), and resection of metastatic lesions. Surgical resection of brain metastases is most likely to benefit those with a solitary lesion in a surgically accessible location, with either no evidence of systemic disease or controlled systemic disease, and with a life expectancy greater than 2 months (104,135,139,140). Unfortunately, only approximately 25% of patients with brain metastases fulfill these indications, as only half of brain metastases are single, and half of single metastases are excluded based on inaccessibility of the tumor, extensive systemic disease, or other factors. In patients who are surgical candidates, resection followed by WBRT has been shown in prospective, randomized studies to improve survival and local control compared with WBRT without surgery. Patchell et al. (135) reported a median survival of 40 weeks in the surgery plus radiotherapy group compared with 15 weeks in the radiation group; recurrence at the original site was 20% and 52% in the surgical and radiation groups, respectively (135). Patients treated with surgery remained functionally independent for a median of 38 weeks versus 8 weeks in the radiated group. An additional benefit of surgical intervention is the tissue diagnosis; in one study, 11% of patients did not have metastatic tumors despite

radiographic findings (135). Surgery alone for a single brain metastasis has a better survival rate than radiotherapy alone, although metastases recur in 70–85% of patients without addition of cranial irradiation (114,136). The combination of surgical resection followed by whole brain irradiation has a median survival of nearly 1 year with improved disease-free survival and functional independence, and decreased rate of death from brain metastases (136,137 and 138).

For most patients, treatment of multiple brain metastases remains WBRT with corticosteroids. Rarely, surgical resection may be considered for easily accessible metastases if other criteria for surgery are met. The contribution of chemotherapy to the management of brain metastases remains uncertain for most types of cancer. Regression of brain metastases has occurred after effective systemically administered cytotoxic chemotherapy (23,24 and 25).

Leptomeningeal Metastases

The syndrome of leptomeningeal metastases (also known as *meningeal carcinomatosis* or *lymphomatous/leukemic meningitis*) refers to diffuse or multifocal seeding of the leptomeninges by systemic cancer (141). Leptomeningeal metastases are identified at autopsy in up to 8% of patients with systemic cancer. The most frequent cancers to metastasize to the leptomeninges are solid tumors, notably breast, lung, melanoma, and gastrointestinal cancers, as well as lymphomas and acute leukemias (142). Primary brain tumors account for 10–32% of cases in some series (142). Acquired immunodeficiency virus–associated lymphomatous meningitis accounted for nearly one-third of cases at one center (143). Some cancers have a high affinity for the nervous system, however, and leptomeningeal disease may be clinically evident in almost half of patients (144). The duration from discovery of the primary malignancy to the diagnosis of leptomeningeal involvement is very broad, from 3 months to 6 years in some series (145).

Two characteristic features suggest a diagnosis of leptomeningeal cancer. First, neurologic dysfunction appears at multiple levels of the neuraxis in the absence of brain or spinal epidural metastases on radiographic examination. The patient may present with a variety of complaints and tends to accumulate new symptoms over weeks as the disease progresses. Second, neurologic signs tend to be much more prominent than symptoms. Although most patients initially complain of symptoms in one anatomical area, examination reveals signs of neurologic abnormality in two or more areas in more than 80% of patients (156).

Symptoms referable to the brain are the initial complaint in approximately half of patients, with headache the single most frequent initial symptom; headache is reported by one-third of patients at presentation (141). The headache can occur in a variety of locations, including bifrontal, diffuse, or radiating from the occipital region into the neck. Nausea or vomiting, light-headedness, and cognitive disturbances are associated features. Changes in mental status alone are a common finding and eventually occur in 80% of patients; these changes are characterized by lethargy, confusion, and memory deficit. Other common cranial symptoms and signs include lateralized weakness, seizures, cranial nerve palsies (most commonly diplopia, hearing loss, and facial weakness) and papilledema. Spinal symptoms due to involvement of the spinal cord or exiting nerve roots and meninges include weakness (lower or upper motor neuron), sensory loss (dermatomal or segmental), pain, ataxia, fecal incontinence, and urinary retention. Occasionally, asymptomatic urinary retention occurs.

The diagnosis of leptomeningeal metastases is based on clinical findings and CSF analysis. The finding of malignant cells in the CSF is the diagnostic gold standard; positive cytology is eventually found in 90% of patients, although three or more examinations of large volumes of CSF may be required (141,145,146). Associated CSF findings include elevated protein, decreased glucose, and lymphocytosis. The CSF levels of these components can vary if sampled at different levels of the neuraxis, with some patients only showing positive cytology if sampled from the ventricular system (147). After two negative lumbar punctures for CSF cytology, it has been recommended to proceed to ventricular or lateral cervical CSF analysis (142). Other biochemical markers of leptomeningeal metastases are used as adjunctive tests, or for serial evaluation of response to treatment (142). Other investigations include flow cytometry of CSF content for evaluation of DNA abnormalities, myelography, a CSF flow study by lumbar or ventricular radioisotope administration, CT of the head, and the most sensitive radiologic examination, MRI of the head and spine with gadolinium (144,145 and 146,148,149,150,151,152 and 153). A pathological diagnosis of cancer with the clinical syndrome of leptomeningeal metastases can also make this diagnosis (142).

Treatment of leptomeningeal metastases is aimed at prolonging survival and improving or stabilizing neurologic disability. Untreated, leptomeningeal metastases from a variety of tumor types have a median survival of 4–6 weeks (154,155). With standard treatment, which is always palliative, survival ranges from 4 to 10 months (156). Meningeal lymphoma and breast cancer have a more favorable prognosis, and may respond to systemic chemotherapy without the addition of intrathecal chemotherapy. Management of leptomeningeal metastases may include radiation therapy to symptomatic sites of the neuroaxis, and intrathecal or intraventricular chemotherapy. Involved-field radiotherapy is recommended if there is associated bulky metastatic disease, regardless of symptoms (145). Craniospinal radiation, used for treatment of leukemic meningitis, is associated with significant systemic toxicity. In general, systemic chemotherapy fails due to poor CSF penetration (142). Intra-CSF chemotherapy, delivered by an Ommaya reservoir, or via lumbar puncture, results in high CSF drug levels without systemic dose-limiting toxicity.

Base of Skull Metastases

The base of the skull includes the temporal, sphenoid, and occipital bones (including the clivus) as well as the bony orbit. Base of skull metastases are most commonly secondary to tumors of the breast, lung, and prostate. Other tumors that may metastasize to the skull base include head and neck tumors, lymphoma, and other tumors that metastasize to bone. The median interval from primary tumor diagnosis to onset of neurologic signs was 23 months in one study; twothirds of patients had metastatic disease elsewhere when the base of skull metastases were diagnosed (157). Several discrete neurologic syndromes have been described, characterized by dysfunction of cranial nerves as they pass through bony foramen. Common areas include the bony orbit, parasellar region, middle cranial fossa, jugular foramen, occipital condyle, clivus, and sphenoid sinus. Base of skull metastases may present with head pain, cranial nerve palsies, or both. Treatment is usually effective and includes pharmacological analgesic interventions (usually nonsteroidal anti-inflammatories with opioids) and focal radiation therapy. Recovery of cranial nerve function tends to be slow.

Cerebrovascular Disease in Cancer Patients

After metastases, cerebrovascular lesions are the next most common neurologic finding at autopsy in cancer patients. In one autopsy series, 14.6% of patients had cerebrovascular lesions (158); of these, approximately half had clinical symptoms of cerebrovascular disease during life. The usual risk factors in the general population for stroke, including age, hypertension, coronary artery disease, and diabetes, are less important in this population than the pathophysiological effects of neoplastic disease and its treatment (159).

Hemorrhagic cerebrovascular events are more common than ischemic events in the cancer population (158). Cerebral metastases and coagulation disturbances, including thrombocytopenia and leukostasis, are the usual causes of intracerebral hemorrhage (ICH) in cancer patients. The reported overall incidence of hemorrhage from an intracranial tumor is 1–15% (160). One neurosurgical series demonstrated an overall tumor hemorrhage rate of 14.6%, of which 5.4% were classified as macroscopic and 9.2% as microscopic (161). As a cause of spontaneous ICH, however, tumor-induced ICH is not a common etiology (only 2% of 461 autopsy cases in one study) (162).

Among all tumor types, those with the highest incidence of bleeding are metastatic melanoma, renal cell carcinoma, germ cell tumors (particularly choriocarcinoma), and bronchogenic carcinoma. The latter is the most common cause because lung cancer is responsible for the majority of brain metastasis (163). Simultaneous hemorrhage into multiple brain metastases occurs frequently (164). The usual presentation mimics an acute vascular event, such as a hypertensive hemorrhage or ruptured berry aneurysm (165). Headache, progressive obtundation, seizures, and focal neurologic signs are reported in two-thirds of cancer patients with intracranial hemorrhage. Hypertensive hemorrhages may be distinguished from intratumoral bleeding by the presence of a history of high blood pressure and location of the hemorrhage in the basal ganglia in 90% of cases. Hypertensive hemorrhage is a relatively rare cause of ICH in the cancer patient (158). Neoplastic aneurysms, although uncommon, are another cause of intracranial hemorrhage in cancer patients.

Coagulopathy may be an indirect effect of the tumor or result from iatrogenic causes, including chemotherapyrelated thrombocytopenia and treatment with warfarin sodium. Disease-related coagulopathy may be consumptive, such as disseminated intravascular coagulation (DIC). Neurologic complications from the latter disorder may be either ischemic or hemorrhagic, including intracerebral bleed and subdural hematoma. Coagulopathy-induced intraparenchymal hemorrhage is most commonly associated with hematological malignancies, especially acute leukemia. Eighteen percent of acute myelocytic leukemia (AML) and 8% of acute lymphocytic leukemia (ALL) patients have ICH found at autopsy (166). The hemorrhage is often large and fatal in AML, yet small and may be asymptomatic in ALL (164). Patients with solid tumors and thrombocytopenia have a low incidence of ICH except when the platelet count falls below 10,000/µl; coagulopathy-related ICH in this population, which may be due to DIC, liver dysfunction, or cancer therapy, usually occurs as a terminal event (160). DIC with ICH is a common cause of death in acute promyelocytic leukemia (167). Anticoagulant-induced intracranial hemorrhage is not common.

Clinically, patients with either spontaneous cerebral hemorrhage from a coagulopathy or hemorrhage into a brain tumor present with a combination of headache, vomiting, seizures, progressive decline in level of consciousness, and focal neurologic deficits. DIC can present with encephalopathy, even in the absence of abnormalities in blood clotting parameters or low platelets. Onset of symptoms may be gradual from coagulopathy-induced ICH, compared to an acute presentation from hemorrhage into a metastatic tumor. Suspected intratumoral hemorrhage should be investigated with CT scan or MRI. Management is primarily medical, and includes ensuring airway control, treatment of severe hypertension, management of elevated ICP, corticosteroids (for tumor edema only), reversal of hemostatic abnormalities (if possible), and antitumor therapy (if appropriate). Surgical evacuation of the hematoma should be considered in selected patients depending on hematoma location and size, patient status, and correctable hematological abnormalities. An intraventricular catheter may be placed for management of hydrocephalus

or increased ICP. Spontaneous ICH in acute promyelocytic leukemia has been reduced significantly with prophylactic heparin, chemotherapy, and transretinoic acid (168,169 and 170).

In patients with leukemia, another cause of ICH is hyperleukocytosis (elevation of the peripheral blast count to greater than 100,000/mm^3 in AML, or 140,000/mm^3 in ALL), which causes early death secondary to ICH in a reported 15% of patients (171,172). Clinically, such patients develop multiple intraparenchymal hemorrhages, occasionally associated with intraventricular or subarachnoid hemorrhage. Chemotherapy and leukophoresis to lower the peripheral blast count can reduce, but not eliminate, the risk of ICH (158,171). Leukostasis can also be treated with radiation therapy (1200–2400 cGy) (155). Blood hyperviscosity can be treated with plasmapheresis or phlebotomy for polycythemia vera (164).

Causes of cerebral infarction in cancer patients include atherosclerosis, nonbacterial thrombotic endocarditis (NBTE), cerebral DIC, venous sinus thrombosis, infection, tumor embolism, and treatment complications. Atherosclerosis and NBTE are the two most frequent causes of cerebral infarction in cancer patients. NBTE causes cerebral infarction by either intravascular microthrombosis or embolism from fibrin and platelet deposition on heart valves (158). NBTE is most commonly associated with adenocarcinoma, especially mucin-producing carcinomas of the lung or gastrointestinal tract. The clinical presentation is usually an acute onset of focal neurologic signs, most frequently aphasia, which either stabilize or progressively worsen. A diffuse encephalopathy also commonly accompanies focal signs. Systemic bleeding, venous thrombosis, and pulmonary embolism are part of the spectrum of coagulopathy that may accompany NBTE. Cerebral infarction from NBTE is suggested by CT or MRI findings of infarction (159). In the absence of associated systemic findings, diagnosis can be difficult. Treatment focuses on the underlying cause of the syndrome; heparin has been shown to improve symptoms from cerebral ischemia but carries the risk of intracerebral and systemic bleeding (159).

Radiation of the head and neck for treatment of Hodgkin's disease, head and neck carcinomas, breast cancer, and primary brain tumors can produce accelerated carotid atherosclerosis, causing symptomatic carotid occlusive disease from 6 months to decades after radiation therapy. The total dose is usually greater than 50 Gy and accelerated atherosclerotic disease is limited to vessels within the irradiated area. There is no association with generalized atherosclerosis beyond concurrent patient-related factors, such as cigarette smoking. The process is accelerated with concurrent hypercholesterolemia (173). The presentation mimics non–radiation-related atherosclerosis and may include transient ischemic attacks, infarction, amaurosis fugax, or seizures. Cerebral angiography shows occlusion or extensive stenosis disproportionately affecting the common carotid artery (174). Although carotid endarterectomy (with or without a patch) remains the standard treatment for this complication, carotid stenting appears to be a safe and efficient treatment for even severe radiation-induced stenosis (175,176,177,178 and 179). Another complication of neck radiation is acute rupture of the carotid artery (which usually occurs after resection of head and neck malignancies), in which necrosis of the skin flap and surgical wound infection have occurred. Although low-dose heparin may reduce the risk of infarction, the prognosis is poor because of potential exanguination or infarction if the carotid artery is ligated (180,181 and 182).

Thrombosis of cerebral venous sinuses or large cortical veins in patients with cancer may be either a metastatic or nonmetastatic complication. In both cases, the superior sagittal sinus is most frequently involved. Metastatic tumor directly causes sagittal sinus thrombosis by either external compression or infiltration of the sinus, which results in stasis or a nidus around which a thrombus may form (183). Nonmetastatic sagittal sinus occlusion may be caused by local injury to the sinus, but is more likely related to a hypercoagulable state of malignancy. Metastatic involvement of the sagittal sinus is seen in lymphoma and some solid tumors, such as neuroblastoma and lung cancer. Nonmetastatic venous thrombosis is less common and occurs in patients with hematological malignancies; it usually is associated with advanced disease. Clinically, nonmetastatic sagittal sinus thrombosis usually presents as an acute onset of seizures, which may be accompanied by encephalopathy and focal signs if infarction has occurred (159). Metastatic sagittal sinus thrombosis presents with subacute signs of increased ICP, such as headache and vomiting; cerebral infarction can also occur. Diagnosis is best made by MRI, magnetic resonance venography, or coronal views during enhanced CT scan. When patients present early in their disease, prognosis is usually good, often with spontaneous recovery. Patients with advanced disease have a poor prognosis. The benefit of heparin in the cancer population is not certain, given the risk of major hemorrhage. Cranial irradiation is indicated for metastatic sagittal sinus thrombosis.

Cerebral hemorrhage or infarction also can occur as complications of treatment of neoplastic disease. Chemotherapy such as asparaginase (superior sagittal sinus thrombosis), mitomycin, and others have been associated with a variety of cerebral complications, either hemorrhagic or ischemic (159,184).

CONCLUSION

Symptoms from neurologic complications of malignancy are common and serious and can be difficult to diagnose. Because of their prevalence and potential for effective palliation, intracranial manifestations of malignancy and their management deserve the attention of all cancer health care providers.

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37

MANAGEMENT OF SPINAL CORD AND CAUDA EQUINA COMPRESSION

SHARON M. WEINSTEIN

EPIDEMIOLOGY

The spine is the most frequent site of bony involvement in patients with malignant metastases (1). The major complications of spinal neoplasm are pain and neurological injury. Compression of neural structures may be caused directly by tumor mass or by displacement of bony fragments into the spinal canal. Tumor of the vertebral bodies has been demonstrated in 25–70% of patients with metastatic cancer (2), and spinal metastases are present in 40% of patients who die from cancer (3). Metastatic lesions are three to four times as common as primary bony tumors of the spine (4).

Each year in the United States, approximately 20,000 cancer patients are treated for malignant epidural spinal cord or cauda equina compression (SCCEC). SCCEC affects 5–10% of adult solid tumor patients and 5% of pediatric solid tumor patients (5,6). This is corroborated by autopsy series (7,8).

Half of patients presenting with SCCEC are not known to have cancer at the time that pain or neurological deficits begin (9).

The distribution of spinal tumors reflects the prevalence of primary malignancies and the physiology of metastasis. Multiple myeloma is the most common primary bone tumor, representing 10–15% of malignant epidural spinal disease. Osteogenic sarcoma is the second most common primary spinal tumor, usually affecting children and adolescents. Fifty percent of chordomas affect the sacrococcygeal bones and 35% affect the base of the skull. Chondrosarcoma and Ewing's sarcoma are other bone tumors that are rarely primary in the vertebrae.

Primary tumors of the breast, lung, and prostate commonly spread to the spinal column. The spine is a frequent site of metastasis of a nonspinal primary osteogenic sarcoma. Spinal metastases are less common in renal carcinoma, melanoma, soft tissue sarcoma, Ewing's sarcoma, germ cell tumors, neuroblastoma, and carcinomas of the head and neck, thyroid, and bladder. Rarely, malignant neoplasms of the brain, pancreas, liver, or ovary affect the bony spinal column. Ten percent of symptomatic spinal metastases originate from unknown primary tumors (3). Some malignancies spread to the intraspinal space without directly affecting bone. Lymphoma and neuroblastoma often invade the spinal canal through the intervertebral foramina. Ewing's sarcoma may be primary in the epidural space, as may osteosarcoma. Primary epidural tumors are rare.

By location, thoracic metastases are estimated to occur twice as frequently as lumbar, and four times as frequently as cervical metastases (10). Almost two-thirds of metastatic spinal lesions present clinically in the thoracic region (11), although in some autopsy series, lesions of the lumbar spine have been most prevalent (3). The level of spinal involvement varies with tumor type. Breast and lung tumor metastases are equally distributed throughout the spine. Prostate, renal, and gastrointestinal metastases are more often found in the lower thoracic, lumbar, and sacral levels. Tumors of the uterus and uterine cervix most commonly spread to the lower lumbar and sacral spine. Pancoast tumors of the apex of the lung extend directly into the cervicothoracic spine in 25% of cases (11), often by intraforaminal extension. Multiple noncontiguous levels of spinal tumor are present in 10–38% of cases (12); this pattern is relatively less common in patients with lung cancer (9).

SCCEC is caused by direct extension of tumor from the vertebral body in 85–90% of cases (11). In pediatric patients, SCCEC due to tumor of the posterior elements is more likely, and intraforaminal spread of tumor from paraspinal sites also occurs more frequently than in adults (12). Tumor metastases to the epidural space seldom breach the dura (3,13).

The prevalence of SCCEC varies according to tumor type. In one series of 103 patients with lung cancer, 26% with squamous histology, 9% with adenocarcinoma, and 14% with small cell tumors had spinal cord compression (14). The prevalence of all neurological complications in this series was approximately 40%.

Breast cancer accounts for almost one-fourth of SCCEC diagnosed in cancer hospitals. Vertebral metastases are identified in 60% of breast cancer patients, and multiple levels of epidural compression are common. SCCEC is rarely the initial presentation or an early finding in breast cancer (15).

Approximately 7% of prostate cancer patients develop SCCEC. SCCEC was noted in 12.2% of patients with poorly differentiated tumors, and 2.9% of those with welldifferentiated tumors (16). The average time from initial prostate cancer diagnosis to SCCEC is 2 years, although it is shorter in stage D2. In approximately 30% of prostate cancer patients with SCCEC, it is the initial manifestation of the cancer (17).

Renal cell carcinomas may also cause SCCEC secondary to bony metastasis. Testicular cancer rarely metastasizes to bone, but may grow into the spinal canal from the retroperitoneal space. Malignant melanoma may produce SCCEC from vertebral disease, but intradural and leptomeningeal involvement are probably more common. Head and neck cancers rarely metastasize beyond the cervical lymph nodes; approximately 80% of distant metastases are detected within 2 years of initial diagnosis. Therefore, a head and neck cancer patient presenting with SCCEC after 2 years should be evaluated for a second primary malignancy. SCCEC occurred at all levels of the spine in one small series of patients with head and neck cancers (18).

Esophageal cancers may rarely cause SCCEC by direct invasion to the thoracic spinal column (19). Carcinoid tumors are associated with neurological complications in less than 20% of cases; the most frequent is SCCEC due to spinal metastases, generally a late complication.

In plasmacytoma and multiple myeloma, SCCEC is usually due to bony collapse, occurring in more than 10% of patients. Hodgkin's disease and non-Hodgkin's lymphomas are associated with a 5% incidence of SCCEC, usually in the presence of extranodal or extensive nodal disease. The thoracic spine is most often involved, in many cases by intraforaminal spread of tumor (20). Patients with SCCEC due to lymphoma are at high risk for meningeal disease. Cerebrospinal fluid (CSF) examination should be considered along with spinal imaging, as concurrent meningeal lymphoma is common and affects the antineoplastic treatment regimen. Vertebral compression fracture with radicular pain is a rare presenting sign of acute leukemia (21).

SCCEC is the presenting sign of cancer in up to 30% of pediatric cases. The time interval to presentation with SCCEC may be twice as long in children without a known cancer, compared to those already diagnosed with malignancy (22). Children without a cancer history presenting with SCCEC are often initially misdiagnosed (23). SCCEC is the most frequent neurological complication of Ewing's sarcoma (24).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of back pain and neurological dysfunction secondary to SCCEC includes benign tumors; meningiomas occur frequently in patients with breast cancer (25). Coexisting nonmalignant disease of the spine may affect as many as 30% of patients with SCCEC (26). Degenerative, inflammatory, and infectious processes affect the spinal structures (27). Soft tissue injuries causing back pain are very common. Trauma is the most common cause of back pain in children; other nonmalignant conditions such as Scheuermann's disease and scoliosis (28) also present in this age group. Back pain in cancer patients may also be caused by

vertebral osteoporosis due to radiation therapy or corticosteroids.

Spinal cord or cauda equina dysfunction may be related to direct tumor or treatment effects, without SCCEC. Leptomeningeal disease, intradural extramedullary or intramedullary spinal cord disease, paraneoplastic necrotizing myelopathy, and myelopathy induced by radiation or intrathecal chemotherapy should be considered if no epidural compressive lesion is found. Myelopathy is a late complication of radiation; epidural lipomatosis may be caused by corticosteroid therapy. Vascular events of the spinal cord may occur in association with tumor masses.

PATHOGENESIS OF NEUROLOGICAL DYSFUNCTION AND PAIN

The high incidence of metastasis to the vertebrae, despite their poor blood supply, is explained by specific physiological features. The vertebrae have a large capillary capacity, promoting local stasis of blood. The walls of the vascular sinusoids are discontinuous and intersinusoidal cords form cul-de-sacs for tumor. Tumor products and the products of bone resorption act to stimulate tumor growth (29). Monocytes producing interleukin-1 may promote resorption of normal bone (30). Metastases may occur more commonly in previously damaged bone (31). Batson's plexus is a valveless system of epidural veins in which blood may flow rostrally or caudally. On Valsalva maneuver, this system drains the viscera and may be a route of metastatic spread. Tumor also reaches bone via the arteries, lymphatics, and by direct extension.

Epidural tumor produces dysfunction of neural structures by direct compression, and by secondary demyelination, ischemia, and tissue edema. Inflammation may change vascular permeability and disrupt the blood–spinal barrier at the tumor site. The release of excitatory amino acids by injured neurons may further promote ischemia and injury.

In the initial stage of epidural cord compression there may be white matter edema and axonal swelling with normal blood flow. These changes are due to direct compression or venous congestion. Over time, progressive compression decreases blood flow and disturbs vascular autoregulation, leading to the development of vasogenic edema. Spinal cord infarction may result from interruption of venous outflow or occlusion of small arteries, or from interruption of the major arterial supply to the spinal cord (including the artery of Adamkiewicz) or radicular arteries in the intervertebral foramina.

A necrotic cavity, usually located in the ventral portion of the posterior columns or dorsal horn, has been visualized on magnetic resonance imaging (MRI) (12). The effects of cord compression may also be due to coup or contrecoup injury, which is not easily predicted on the basis of tumor location in relation to spinal cord. Demyelination as a mechanism of neural dysfunction (5) is supported by pathological examination, which demonstrates greater demyelination of white matter than gray matter, a pattern that does not conform to arterial supply. Animal experiments indicate that more rapid ischemic change produces a greater degree of irreversible neurological injury (32,33). Similar observations have been made in the human spinal cord.

Pain due to malignancy of the spine may result from activation of afferent nociceptive neurons by mechanical distortion and inflammatory mediators (nociceptive pain) or from neural dysfunction (neuropathic pain). Nociceptors innervate the periosteum, soft tissues (ligaments and muscles), facet articular cartilage, dura mater, nerve root sheaths, and blood vessels. Vertebral collapse and structural instability can give rise to mechanical pain through injury to these structures, which worsens during spine loading and weight shifting. There may be secondary myofascial pain as well. Neuropathic pain results from altered peripheral and central neural activity that may be induced by injury of the nerve roots, axonal injury, or other processes such as deafferentation.

PATIENT EVALUATION

Although it is widely recognized that pain is often the first symptom of spinal neoplasm, accurate assessment of back and neck pain in the cancer patient may be challenging to even the experienced clinician. A complete history and physical examination, including thorough neurological examination, are essential to localize the underlying pathology. Proper clinical localization is necessary to choose diagnostic and therapeutic interventions correctly (Table 37-1). Inadequate evaluation increases the likelihood of otherwise preventable neurological compromise. In a retrospective survey of cancer patients presenting with back pain, misdiagnosis was attributed to poor history, inadequate examination, and insufficient diagnostic evaluation (34). In a review of cancer pain consultations performed by a neurology-based pain service, the comprehensive evaluation of pain led to an identification of new malignant involvement in 65% of cases (35).

Bone
Bone alone
Single site
Multiple contiguous sites
Multiple noncontiguous sites
Bone and paraspinal soft tissues
Bone, paraspinal tissues, and viscera
Bone and nerve roots
Bone and epidural space (without thecal compression)
Bone and epidural spinal cord compression
Bone and epidural cauda equina compression
Epidural
Intraforaminal
Isolated
Local extension
Epidural and spinal cord compression
Single site
Multiple contiguous sites
Multiple noncontiguous sites
Epidural and cauda equina compression
Single site
Multiple contiguous sites
Multiple noncontiguous sites
Diffuse

TABLE 37-1. PATTERNS OF SPINAL TUMOR INVOLVEMENT

History

Up to 95% of adult and 80% of pediatric patients with SCCEC present with pain (12,36). The difference in pain prevalence between adults and children may reflect greater difficulty in pain assessment and underreporting of pain in children. Pain may precede other symptoms and signs by 1 year (12). This interval may vary by tumor type; it is generally shorter for lung cancer than breast cancer (37). Overall, patients experience pain for an average of 4–5 months before presentation (3).

Pain may be local at the site of pathology or referred in a nonradicular distribution, a radicular (dermatomal) distribution, or have combined features. Radicular or root pain is reported in 90% of lumbosacral SCCEC, 79% of cervical, and 55% of thoracic cord compression (37). Radicular pain may be bilateral in thoracic lesions, and is often described as a tight band around the chest or abdomen. It is important to note that radicular pain may be experienced in only one part of a dermatome. When a nerve root lesion produces chest or abdominal pain, the complaint may be mistakenly identified as referred pain of visceral origin. Radicular lesions are usually associated with segmental findings on examination. Nonradicular referred pain may be associated with vague paresthesias and tenderness at the painful site. Pain may be continuous at rest and markedly aggravated by body movements (incident pain). Although local pain from a vertebral lesion is worsened with loading due to upright posture, pain due to SCCEC is often greatly increased by lying supine. A lesion confined to the vertebral body may also produce nonradicular referred pain. Disease at C7 may refer pain to the interscapular region, and pain due to disease at L1 may be referred to the iliac crests, hips, or sacroiliac region. Sacral disease often causes midline pain radiating to the buttocks, which is made worse with sitting. Radicular pain in particular may be paroxysmal, spontaneous, or provoked by movement or sensory stimulation. Valsalva maneuver may produce or aggravate both local and radicular pain. Pain on neck flexion or straight leg raising implies dural traction. Lhermitte's sign (electric shock-like pain) indicates a spinal cord lesion. Compression of the cervical spinal cord rarely produces funicular pain, which is pain referred to the lower extremities, thorax, or abdomen as a band of paresthesias. “Pseudoclaudication” of legs may be an isolated lumbar root symptom (38).

The neurological findings associated with SCCEC also vary. There can be extensive epidural tumor with no neurological findings on examination. Upper motor neuron weakness may occur with lesions of the spinal cord (above the L1 vertebral body). This finding is present in 75% of patients with SCCEC at diagnosis (11). Sensory changes occur in approximately half of patients at presentation, including paresthesias and sensory loss, which can be segmental or below the level of injury. Sensory complaint without pain is exceedingly rare. Bladder and bowel dysfunction are evident in more than half of patients on presentation with SCCEC; constipation usually precedes urinary retention or incontinence (39).

Examination

The physical examination begins with observation of posture, spinal curvature, symmetry of paraspinal muscles, extremities, and skin. The practitioner may appreciate tenderness of the spinous processes on palpation or percussion, although this may not correlate with the level of spinal disease. Gibbus deformity and vertebral misalignments are frequently palpable; actual crepitus of the spine is unusual. Tenderness or spasm of the paraspinal muscles may also be noted. Urinary retention may be demonstrated by bladder percussion. Laxity of the anal sphincter may be apparent on digital rectal examination. Specific areas of sacral or coccygeal

tenderness may be identified by external palpation, rectal, or pelvic examination.

Spinal maneuvers to elicit pain should be performed carefully. Thoracic and abdominal radicular pain may be provoked on lateral flexion and rotation of the trunk. Increased pain on neck flexion and straight leg raise sign may be “pseudomeningeal” signs of dural traction due to epidural tumor. If neck rigidity is present, the examiner should use extreme caution with range-of-motion maneuvers. Muscle spasm may be triggered by bony instability of the cervical spine, and forced movements may dislodge bony fragments, causing acute spinal cord or brainstem injury.

The neurological examination reveals positive findings in the majority of patients with SCCEC. The examination should include assessment of mental status, cranial nerves, motor function, reflexes, sensation, coordination, and gait. Proximal lower extremity weakness may be initially evident only as difficulty rising from a chair. Although weakness due to upper motor neuron dysfunction is usually associated with increased tone and hyperreflexia, acute “spinal shock” can cause a flaccid areflexic paralysis. In the subacute phase of recovery from spinal shock, “mass reflexes” appear consisting of flexor spasms, hyperhydrosis, and piloerection due to autonomic dysfunction. Lower motor neuron weakness may be accompanied by flaccidity, atrophy, muscle fasciculations, and hyporeflexia. A cervical lesion can produce segmental hyporeflexia in the arm or arms and increased reflexes below. Lesions above the pyramidal decussation of the corticospinal tracts in the lower brainstem may be associated with loss of contralateral abdominal reflexes; lesions below the decussation produce loss of ipsilateral abdominal reflexes. Segmental motor dysfunction due to thoracic nerve root disease may produce asymmetric abdominal muscle contraction and loss of abdominal reflexes. Beevor's sign (upward movement of the umbilicus on attempted flexion of the trunk) indicates a lesion at or near the T10 level. Lesions of the roots of the upper lumbar plexus produce hip flexion weakness and a dropped knee jerk reflex; lesions of the roots to the lower lumbar plexus may produce foot drop and diminished ankle jerk reflex. Loss of bulbocavernosus and anal reflexes may accompany conus and cauda equina lesions (39).

Although the sensory examination may help in determining the level of epidural disease, SCCEC results in a broad variation of sensory dysfunction, with incomplete lesions the rule. The level of reduced sensation may be determined to be up to five segmental levels below, or one to two segments above, the level of cord compression. A sensory level on the trunk sparing the sacral dermatomes may occur in up to 20% of patients with thoracic or high lumbar compression (40). Suspended partial sensory levels, or unilateral bands of sensory loss may be seen with spinal cord lesions up to the brainstem. Compression of the conus of the spinal cord may produce sensory loss in the saddle area (buttocks and perineum). Facial numbness may be due to upper cervical lesions. Lesions of the upper thoracic nerve roots may result in Horner's syndrome, with autonomic dysfunction of the face and upper extremity.

Gait ataxia is an uncommon isolated sign of spinal cord compression. Other unusual features are signs of raised intracranial pressure; facial paresis, lower extremity fasciculations or sciatica with cervical tumor; nystagmus with thoracic tumor; spinal myoclonus; an inverted knee jerk reflex; and “painful legs and moving toes” (12).

Diagnostic Evaluation

The selection of specific imaging tests is guided by the clinical presentation. Several imaging methods are available to confirm SCCEC. Because the correct interpretation of symptomatic and asymptomatic lesions on diagnostic imaging studies requires thorough knowledge of the patient's clinical presentation, it is strongly recommended that clinicoradiographic correlation be made by the examining physician. In each individual case, the “neurological urgency” for further diagnostic tests must be modified according to the potential for treatment, the patient's condition, and overall prognosis (Fig. 37-1).

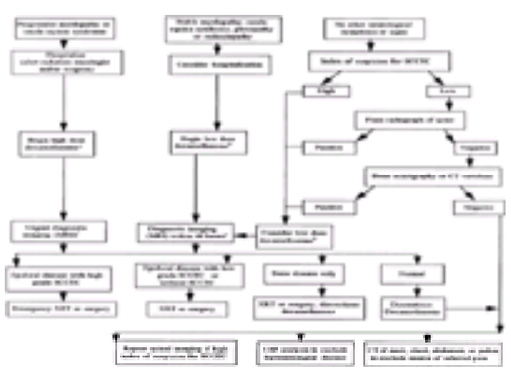

FIGURE 37-1. Cancer patient with back or neck pain—candidate for radiotherapy or surgery. CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; SCCEC, spinal cord or cauda equina compression; XRT, external beam radiotherapy. [a]High-dose dexamethasone, 100 mg followed by 24 mg q 6h with taper over weeks. [b]Low-dose dexamethasone, 20 mg followed by 4 mg q 6h with taper over weeks. [c]MRI, suggest sagittal screen of vertebral column with expanded imaging of affected areas or CT myelography (see text). (Data from Foley KM. Pain syndromes in patients with cancer. In: Portenoy RK, Kanner RM, eds. Pain management: theory and practice. Philadelphia: FA Davis Co, 1995:195; and Posner, JB. Neurological complications of cancer, contemporary neurology series vol 45. Philadelphia: FA Davis Co, 1995:112, with permission.)

Plain radiographs confirm tumor and assess structural stability of the spinal elements. In the cancer patient at risk for spinal metastases with neck, shoulder, or upper extremity pain, flexion and extension views of the cervical spine should not be forced. Although plain radiographs are over 90% sensitive and 86% specific for demonstrating abnormalities in the patient with symptomatic spinal metastases, autopsy series suggest that up to 25% of spinal lesions are invisible on radiography (41). False-negatives occur due to mild degree of pathology, poor visualization (e.g., the first thoracic vertebra), or because the abnormality is missed on interpretation. The false-positive rate for interpreting collapsed vertebrae as malignant may be as high as 20% (42).

It is estimated that a 30–50% change in bone mass is needed before plain films become abnormal (36). On anterior/posterior view, spinal radiographs may show pedicle erosion (the “winking owl” sign), increased interpeduncular distance, paraspinal widening, or paraspinal soft tissue shadow. On lateral view, vertebral collapse (wedging of the body), scalloped bodies, disc space destruction, a narrow spinal canal, hypertrophied facets, and disc calcification may be seen. Oblique views are needed to discriminate spondylolytic osteophytic encroachment from tumor causing foraminal abnormality (5). Greater than 50% vertebral collapse and pedicle erosion are especially predictive of SCCEC. On plain radiography, multiple vertebral involvement is noted in up to 86% of patients with spinal tumor (5), and in greater than 30% of patients with SCCEC.

Computed tomography (CT) may be useful to better delineate pathology using restricted fields of view (41). CT is superior to other imaging techniques for demonstrating cortical bone architecture (43). Before the availability of MRI, CT in combination with myelography was considered the gold standard for demonstrating the level and extent of epidural disease. CT-myelography may be considered if the index of suspicion for epidural disease is high and other imaging studies are normal, or if MRI cannot be interpreted or performed. Lumbar puncture should precede cervical puncture in most cases. Injection of air to supplement contrast medium may better image CSF block. If the upper and lower extent of the block cover a long spinal segment, myelography may be repeated after treatment to determine if multiple discrete lesions are present and to better define radiotherapy portals. If repeated imaging is anticipated, oil-based contrast medium may be used to allow for follow-up radiographic imaging without repeated punctures. Another advantage of myelography over other diagnostic imaging tests is the collection of CSF for analysis. However, there is a risk of worsening neurological function after dural puncture in the patient with partial CSF block, due to “coning” of the spinal cord as pressure below the block is relieved. This risk may be as high as 15% (12,44). It is therefore recommended that under these conditions, corticosteroids be administered before dural puncture.

Radionuclide bone scintigrams reveal a 5–10% change in bone tissue (36). Bone scintigrams are more sensitive than radiographs except in multiple myeloma (12). They are not as specific as radiographs in identifying the level of SCCEC. False-positives may be due to nonmalignant skeletal conditions, and false-negatives may be due to lytic lesions, e.g., myeloma or solid tumors such as lung and melanoma, and prior radiation therapy. If the entire skeleton is involved by tumor, no contrast in the radionuclide uptake can be appreciated. New technology of immunoscintigraphy may prove to be more sensitive (41).

MRI is now considered by many experts to be the imaging procedure of choice for SCCEC. MRI without contrast enhancement may eliminate the need for other imaging studies. MRI sensitivity and specificity rival that of CT-myelography and are better with contrast. In the patient with back pain and radicular symptoms but no bony tumor on plain radiograph, gadolinium-enhanced MRI is indicated to identify intraforaminal disease such as occurs in lymphoma and some solid tumors (36). Double-dose gadolinium-enhanced MRI may increase accuracy. MRI with and without contrast excludes vertebral metastases, paravertebral lesions, SCCEC, intramedullary tumor, and many leptomeningeal processes. Fat-suppression and T-2 weighting, not supplemented by addition of contrast, may improve detection of myeloma lesions (45). In previously irradiated bone, MRI signal intensity is increased and gadolinium contrast enhancement is decreased.

In the cancer patient with back pain and suspected SCCEC, complete spine MRI is indicated when there is high risk of noncontiguous or skip lesions. A full spine sagittal “screening” image to identify targets for more detailed imaging is suggested (5). Often the cervical spine is not imaged because it adds significantly to

sequencing time. Failure to identify multiple levels of SCCEC may compromise radiotherapy if untreated lesions become symptomatic and are detected at a later time. The cost-effectiveness of sagittal screening studies for identifying treatable lesions has not yet been determined. In patients with claustrophobia or severe pain in the supine position, conscious sedation or general anesthesia may be required to complete the MRI. The risk of sedation or anesthesia for MRI must be weighed against the risks of alternative imaging procedures, such as CT-myelography, for each individual patient.

CSF examination is not required for the diagnosis of epidural tumor, and as noted above, dural puncture may pose some risk to the patient with SCCEC. CSF analysis may show elevated protein with normal glucose, and rarely, pleiocytosis.

The patient presenting with MESCC and an unknown primary tumor generally undergoes a battery of tests to identify the primary neoplasm. At times, biopsy of a vertebral, epidural, or paraspinal lesion is needed to determine the tumor histology.

MANAGEMENT OF ACUTE SPINAL CORD OR CAUDA EQUINA COMPRESSION

Pharmacological Interventions

Corticosteroids are the mainstay of pharmacological therapy for acute SCCEC. The administration of these agents prevents lipid peroxidation of neuronal cell membranes, ischemia, and increased intracellular calcium (46). Vasogenic edema in SCCEC has been demonstrated to be responsive to corticosteroids. Cytotoxic edema may also play a role. Alternative steroids and other agents to treat edema, such as mannitol, may be used.

The timing of administration and dosage of corticosteroids may affect neurological outcome, and there is some evidence for a therapeutic window (38,46). Better analgesic effect of higher-dose regimens has been demonstrated in one study (47). Many authors favor a prolonged course of high-dose corticosteroids, e.g., the equivalent of a bolus of 100 mg dexamethasone followed by 96 mg per day in divided doses, tapered over a few weeks for high-grade SCCEC, and a lower dosage, e.g., 20 mg dexamethasone followed by 16 mg per day in divided doses with a taper, for low-grade SCCEC (5,47,48).

High-dose therapy may be more analgesic, but increases the risk of side effects. Side effects depend on duration of drug administration, cumulative dose, and regimen. In one prospective study of SCCEC patients treated with highdose corticosteroids, it was noted that depressive symptoms and disorders were more common than in similar patients not receiving such treatment (49). Suppression of the hypothalamic-pituitary-adrenal axis occurs with sustained dosing; it is suggested that dosing be readministered after withdrawal in situations of severe physiological stress. Steroid-induced osteoporosis may be reversible in the young (50). Other withdrawal symptoms, including *Pneumocystis* infection, have been reported. Corticosteroids are metabolized by the cytochrome P450 system, which has implications for drug interactions with anticonvulsants and other medications; this potential interaction with anticonvulsants may be least with valproate sodium (46). Clinicians should be aware that rapid administration of steroids causes severe burning pain in the perineum; therefore, it is preferable that doses not be given as intravenous push. Except in emergency situations, corticosteroids should be held before making the cancer diagnosis if lymphoma is suspected due to the immediate oncolytic effect, which would impede diagnosis.

Virtually all patients presenting with SCCEC have severe pain requiring opioid analgesics. Practitioners should be prepared to titrate opioid to effect; this may require high doses, especially in patients with neurological involvement (51).

Nonpharmacological Interventions

Radiation Therapy

Radiation therapy for SCCEC is chosen to inhibit tumor growth, restore and preserve neurological function, treat pain, and improve quality of life. The course of external beam radiotherapy (XRT) for spinal metastases and SCCEC depends on the radiosensitivity of the tumor and its extent. Currently, XRT is considered by many clinicians to be the primary treatment for SCCEC. The course may be accelerated for patients in severe pain. The spinal section routinely treated includes two vertebral segments above and below a single site of neurological compression. Anterior/posterior portals are set to include the vertebral body, especially in low thoracic and lumbar lesions. Fields are also designed to accommodate paravertebral tumor. A single port field can be used in very cachectic patients. As there are no known predictive factors for epidural progression with multiple sites of spinal disease, the decision to treat asymptomatic noncontiguous sites depends on clinical judgment. In addition to clinical condition of the patient, factors to be considered include the type of tumor, presence of vertebral collapse, and anticipated future difficulty in matching radiation portals. Special techniques are required to reirradiate. XRT alone is more than 85% effective for SCCEC in radiosensitive tumors (3). Motor improvement is seen in 49% and stabilization of function in another 31% of patients. However, less than 50% of patients regain lost function (3). The possibility of progression to SCCEC may be reduced by irradiating bony lesions. It is uncertain if radiation is treating micrometastases or preventing them. The response to XRT may be delayed in some cases; the factors accounting for this observation are not well understood (52). Brachytherapy can be used for adjacent paraspinal masses and may prevent SCCEC (53).

Surgery

Surgical intervention for SCCEC may be performed to (a) establish the cancer diagnosis when it is in doubt and tissue is required for histological examination, (b) achieve surgical cure for a primary neoplasm, (c) treat prior irradiated radioresistant tumor with symptomatic progression of SCCEC, (d) decompress neural structures and stabilize the spine, or (e) halt a rapid clinical deterioration (3,54,55 and 56). The specific goals of surgery are to resect pathology, restore load-bearing capacity, decompress neural structures, achieve stability, treat pain, and improve quality of life.

Many factors affect choice of surgical technique, including tumor location, tumor extent, integrity of adjacent segments, and general debility. In vascular tumors such as renal and thyroid, operative intervention may be preceded by vascular embolization. Tumor decompression and stabilization may be achieved through either an anterior vertebrectomy or laminectomy. Posterior decompression through wide laminectomy is generally followed by stabilization to prevent kyphosis (57,58,59 and 60). New posterolateral techniques are being developed for specific SCCEC syndromes in advanced cancer patients.

In one thorough retrospective study (61) of 110 patients after aggressive surgical intervention for spinal metastases, 82% of patients showed improvement in pain relief and ambulatory status. The goals of treatment were identified as gross total resection of tumor and spine reconstruction. Half of the patients had prior treatment and were deteriorating clinically. The “traditional” criteria for surgery, such as relapse after radiation therapy and for determination of histology, were expanded to include gross tumor resection for radioresistant or solitary lesions and for spinal stabilization. In this series, more complex surgical instrumentation was used than previously reported. Most patients received ongoing systemic therapy, partly confounding the analysis of long-term outcomes. The complication rate of 48% correlated with age older than 65, prior spinal treatment, and the presence of paraparesis. These factors also correlated with greater morbidity and poorer survival. However, in this series, nearly half of the patients were alive at 2 years, an improvement over prior studies that had compared the posterior surgical laminectomy and radiation therapy to radiation therapy alone. This improvement in survival was noted in patients with more advanced cancer and prior treatment. These authors concluded based on prior reports (62,63) and the data from this series that the anterior surgical approach with stabilization may improve outcomes, and suggested further definition of the subset of patients that might benefit from early anterior resection and spinal stabilization.

Early reviews of surgical outcomes have confirmed higher morbidity and mortality in patients with prior spine irradiation, age older than 70 years, and those with poor performance status at the time of surgery (64). In a recently reported series, the factors predictive of shorter survival were poorer preoperative neurological status (leg strength grade 3/5 or weaker), anatomical site of the primary carcinoma (lung or colon cancer), and multiple vertebral body involvement. These authors consider surgical intervention contraindicated if two or more of those factors are present (63). Several authors have suggested that a limited posterolateral approach to tumor resection be reserved for patients with expected survival less than 6 months (61,65). Few data are available regarding surgical intervention for lateral epidural or intraforaminal disease. In a recent experience, a small group of patients, not considered candidates for major surgical procedures, benefited from limited resection of lateral epidural tumor. Surgery was preceded by careful correlation of symptoms with tumor mass, and good outcomes were recorded in all eight patients (65). This experience supports careful consideration in each case until criteria for primary surgical intervention are more fully delineated. Further refinement of surgical approaches also depends on precise neuroanatomic localization of neoplastic involvement (Table 37-1).

The complication rate for spinal surgery may be as high as 30% in patients who have undergone prior XRT (3). Coagulopathy and exogenous anticoagulants increase the risk of hematoma at the operative site. Difficult wound healing, infection, bony instability, nonfusion, displacement of implants, and other complications may occur.

There has been a steady evolution in the concepts and execution of surgical management for SCCEC. In choosing primary surgical versus radiotherapeutic intervention, the prognosis for neurological improvement and expected impact on functional status must be considered. In some series, radiation therapy has been shown to be equally effective to laminectomy and radiation, but with less than 50% neurological improvement overall (11). De novo anterior-posterior resection with spine stabilization may result in better outcomes than laminectomy and radiation or radiation alone, as surgical complications are generally manageable, survival is improved (although the 2-year survival for lung cancer may be 10% and for colorectal cancer only 17%), and patients may remain ambulatory longer (61). The data are as yet insufficient to draw final conclusions regarding pain and quality of life outcomes. The decision to recommend initial radiation therapy versus surgical intervention

must be individualized. It has been suggested that without bony instability, the speed of progression of neurological deficit and radiosensitivity of the tumor are the main factors to consider. Severe deficits hold a poor prognosis independent of treatment.

Nonsurgical stabilization of the bony spine can be accomplished with a cervical collar or body bracing. The cancer patient with neck pain and suspected cervical spine disease should be placed in a collar while diagnostic evaluation is being conducted.

ONGOING CARE

Pain Management

Extended corticosteroid administration (i.e., for the duration of life in patients with SCCEC and short prognosis) has not been well studied but is common in clinical practice. This practice should be discouraged unless there is evidence of ongoing steroid-reversible neurological deficits, due to the high risk of steroid toxicities discussed in the section Pharmacological Interventions (66).

Guidelines for the use of nonsteroidal anti-inflammatories, opioids, and adjuvant analgesics for neuropathic pain have been published in recent years (67,68,69,70 and 71). Chronic opioid therapy is often required for persistent pain after treatment of SCCEC. Cases have been reported in which patients with SCCEC required prolonged high-dose intrathecal infusion of opioid and local anesthetic to obtain adequate analgesia (72,73). Radionuclides are discussed in other chapters.

Neuroablative procedures are considered when the benefit to risk ratio favors analgesia over the potential for further neurological compromise. Destruction of nervous tissue may be accomplished by anesthetic or surgical means. Chemical epidural neurolysis may be chosen to effect single or multiple nerve root interruption. Intrathecal neurolysis would be anticipated to achieve analgesia over a wider territory, and may be selected when the epidural space is compromised. Both approaches entail risk of acute neurological deterioration, which may be irreversible (74). Neurosurgical ablation of nerve roots (rhizotomy) involves major surgery, and is less often indicated in very sick patients. Midline myelotomy may be indicated for patients with severe midline sacral pain and bladder or bowel compromise due to tumor of the sacrum. Spinothalamic tractotomy or cordotomy, although more easily performed as a percutaneous procedure, is not generally useful for pain in association with spine disease or SCCEC. Hypophysectomy for diffuse painful metastatic bone disease may yield success rates as high as 90% in some endocrine responsive tumors (75).

Integration of pharmacological and nonpharmacological analgesic therapies is needed for the vast majority of patients with SCCEC. A multidisciplinary approach to pain management and rehabilitation of patients with resected sacral chordoma has been reported (76).

Rehabilitation

Each patient's rehabilitation program must be individually tailored and continually reassessed and modified. For some patients, comprehensive care may be best accomplished in a formal rehabilitation setting (77). Specific rehabilitation goals are to improve ambulation, achieve weight bearing and transfers, restore bladder and bowel function, and protect the skin.

Spinal orthotics stabilize the spine and may decrease spinal pain by limiting motion. Physical therapy techniques for pain include massage, ultrasound, and transcutaneous electrical nerve stimulation.

Approximately 50% of patients require urinary catheterization before and after XRT for SCCEC (3). Sexual dysfunction may be treatable with specific physical interventions.

A number of medical problems common to the cancer population may limit aggressive rehabilitation efforts. Organ failure due to the disease or its treatment, poor nutrition, and multiple physical and psychological symptoms may complicate rehabilitation. An active exercise program may have to be modified. Weakness due to spinal cord or nerve root compression may be complicated by peripheral neuropathy or myopathy, which are common complications of antineoplastic treatment. The skin of many cancer patients is relatively more prone to breakdown and infection. Skin care and protection are essential, especially in the bedridden patient.

Chronic musculoskeletal problems may occur in children after spine irradiation during growth, due to the development of secondary spinal deformities. The risk of fracture in osteoporotic or tumor-laden bones should be carefully evaluated before initiating a mobility program. In paraparetic or paraplegic patients, prophylactic fixation of upper extremity lesions may be considered to aid mobility and weight bearing. In bedridden patients with multiple impending fractures, positioning and transfers must be undertaken with great caution.

The goals of physical medicine and rehabilitation in the patient with SCCEC range from active programs to supportive care (78). Preventive rehabilitation therapy is directed toward achieving maximal functional restoration in patients cured or in stable remission from their cancer. Continued encouragement for the effort required in aggressive rehabilitation is needed for a progressive decline in function due to advancing disease. For patients with limited prognosis, usually considered as less than 6 months life expectancy, family participation receives more emphasis. The needs of the patient trend toward more dependent care as cancer progresses. Palliative rehabilitation interventions are intended to provide comfort in the terminal stages of cancer.

Psychological Interventions

Ongoing psychological support of the patient with metastatic spine disease is essential. Issues of loss of independence and loss of function require careful attention. Families often benefit from emotional support for anticipatory grieving. Professional assistance is indicated as the burden of care increases with a patient's progressing disease.

CLINICAL OUTCOMES

The potential for recovery of function in patients with tumor involvement of the spine and associated neurological structures varies by tumor type (primary or metastatic), the number of vertebrae involved, the nature and degree of neurological involvement, the oncologic status, and general medical condition. In most series, approximately 50% of patients with metastatic spine tumors are ambulatory at presentation, 35% are paretic, and 15% are plegic (38). Up to 30% of patients with weakness become plegic within the first week of presentation (5). The prognosis for regaining ambulatory status in SCCEC patients who begin therapy while ambulatory is 75%; prognosis declines to 30–50% for patients who begin therapy paretic, and to 10% for those who begin therapy plegic (36). The duration of neurological symptoms before treatment also affects prognosis for neurological recovery. If paraplegia has been present for days, or urinary retention present for more than 30 hours, the likelihood of recovery is decreased (79). Rapidly progressing symptoms confer a worse prognosis.

Patients who remain unable to ambulate after irradiation for SCCEC have a particularly poor prognosis for survival, due to complications of paresis and more advanced disease. Survival rates for patients with SCCEC are 40% at 1 year if ambulatory before and after radiation treatment, whereas patients who are nonambulatory before and ambulatory after treatment have a survival rate of 30% at 1 year and 20% at 3 years. Prognosis falls to 7% at 1 year for patients who are nonambulatory after treatment (3).

Response to treatment for SCCEC and survival vary with the nature of the malignancy. In patients with prostate cancer, the response to treatment of neurological complications depends on whether the patient has received prior hormonal therapy. Better response to hormonal manipulation correlates with longer survival. The median survival of prostate cancer patients after diagnosis with SCCEC is 6 months; only 34% survive at least 1 year (80). Renal cancer is poorly radioresponsive, and median survival time after diagnosis with SCCEC is less than 4 months (81). Hemorrhagic complications of spinal surgery for metastatic renal tumor may be avoided by preoperative embolization (82). In testicular cancer, chemotherapy is effective for untreated lesions or for responsive tumors (83), but radiation and surgery may be considered if the disease is not chemoresponsive (81). Up to 75% of melanoma patients with SCCEC respond to radiation therapy (84,85 and 86.) Patients with carcinoid tumor and SCCEC have a median survival of 6 months. Ambulatory status may be preserved with radiation in up to 90% of patients with carcinoid tumors (19). In myeloma, long-term survival is common. In a series of patients with multiple myeloma, the 1-year survival was 100% and median survival 37 months after SCCEC was diagnosed (87). Solitary plasmacytomas are generally irradiated and surgically removed. Multiple myeloma patients often receive radiation therapy to maximum spinal cord tolerance before surgical intervention is considered. Most lymphomas respond to chemotherapy and radiation. In pediatric patients, surgery may be preferred for radioresistant sarcomas and small cell tumors (Ewing's sarcoma, neuroblastoma, lymphoma, and germ cell tumors) presenting with rapid neurological deterioration. A trend toward extended survival has been shown after surgical decompression in Ewing's sarcoma. Many small cell tumors respond to chemotherapy or radiation. Younger age may confer greater risk of radiation complications (88). Complete resection of primary spinal extraosseous epidural Ewing's sarcoma may be difficult. The 18-month survival was less than 40% in a small series of patients with this unusual malignancy (89).

The survival prognosis for all patients treated for SCCEC is less than 50% at 2 months (11). Definitive intervention for SCCEC must therefore be considered in the context of the patient's overall disease status. Systemic antineoplastic therapy may at times precede or entirely supplant intervention targeted at SCCEC. For patients

with very advanced cancer, the burden of intervention to reverse SCCEC often outweighs minimal potential gains in function. Although few studies of quality of life have been conducted in this population, pain control should remain a high priority regardless of prognosis. Given limited available data, the clinician caring for patients with spinal neoplasm must carefully select medical interventions to achieve therapeutic goals for each individual patient and family.

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38

NEUROMUSCULAR DYSFUNCTION AND PALLIATIVE CARE

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The neuromuscular disorders experienced by cancer patients may cause weakness, fatigue, sensory loss, and pain, including cramps and dysesthesias. To determine the etiology of these symptoms accurately and formulate a treatment strategy, physicians need a logical approach to assessment. First, a careful history and neurological examination are needed to identify potential neuromuscular dysfunction, presenting as part of the complex set of symptoms that occur with cancer. Second, a specific diagnosis is established through laboratory testing or appropriate consultation. Finally, appropriate therapy is prescribed. In this chapter, such an approach is explored with reference to common cancer-associated neuromuscular diseases.

DEFINITIONS

The term *neuromuscular* refers to both the muscle and the peripheral nervous system, which includes the anterior horn cell, the dorsal root ganglion, the sensory and motor nerve roots, the plexi, the peripheral nerves, and the neuromuscular junction. Patients with cancer can develop neuromuscular dysfunction through direct compression or invasion of these structures by neoplasm, toxic effects of antineoplastic therapies, or paraneoplastic effects.

HISTORY AND EXAMINATION

A careful history and examination of the patient complaining of fatigue, weakness, sensory abnormalities, or pain help the practitioner differentiate a neuromuscular problem from disturbances caused by central nervous system (CNS) or nonneurological dysfunction. The tempo of symptom onset is important. Weakness or sensory dysfunction that develops abruptly may indicate a vascular injury in the central or peripheral nervous system, tumor impingement on neural structures, or a fulminant autoimmune or inflammatory process. Patients with recent onset, rapidly progressive neuromuscular symptoms require immediate attention. Regardless of tempo of onset, symptoms should be assessed in the context of the location and nature of the underlying malignancy, and previous or current treatments and medications.

The nature and distribution of symptoms offer further diagnostic clues. For example, both positive (e.g., tingling or pain) and negative (e.g., numbness) sensory complaints are common with peripheral nerve injury. Motor weakness of one side of the body suggests a CNS lesion, whereas weakness of distal leg and hand muscles often is caused by a neuropathy. Proximal weakness is more typical of myopathies or defects of neuromuscular transmission. Distal weakness is more typical of a neuropathy. Similarly, a sensory level over the trunk is typical of spinal cord compression, whereas foot and hand numbness in a stocking/glove pattern is more typical of a neuropathy. Reflexes are usually brisk when weakness is caused by a CNS lesion and reduced in cases of neuropathy. Reflexes are often normal in myopathy but may be reduced if the myopathy is severe.

The physical examination is generally not definitive, and other diagnostic procedures should be used to confirm the diagnosis. Electrodiagnostic studies frequently can help to localize the dysfunction. Additional laboratory studies, such as hemoglobin A1C, thyroid function tests, vitamin B_{12}, Lyme antibody titers, cryoglobulins, and serum protein electrophoresis, may allow a specific diagnosis to be made. Even when the primary diagnosis is clear, testing for treatable contributing factors should be performed. If found, these other potential causes of neuromuscular dysfunction should be treated to prevent further deterioration.

Table 38-1 presents the symptoms that may be caused by neuromuscular dysfunction and the most typical neuromuscular disorders causing those symptoms. Some of the symptoms, such as fatigue and diffuse weakness, do not help localize the defect. Others, such as muscle tenderness or focal pain, may lead to an anatomical localization.

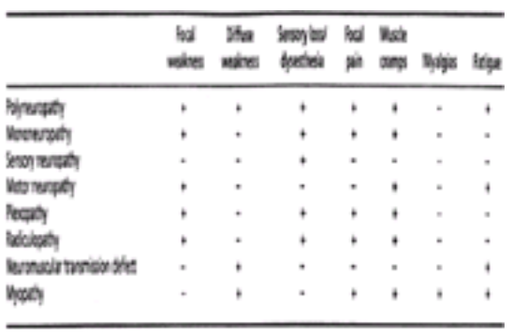

TABLE 38-1. CARDINAL SYMPTOMS OF NEUROMUSCULAR DYSFUNCTION (MOST SYMPTOMS ALSO HAVE A LARGE NUMBER OF NONNEUROMUSCULAR CAUSES)

TREATMENT

Treatment strategies for neuromuscular disorders fall into two categories: etiological and symptomatic. With our current state of knowledge, reversal of disease with effective etiological therapy is rare. When available, etiological treatments are presented with the description of the specific disease entity. Symptomatic therapy, which is becoming more effective, is presented as a separate section. One important general point is that damaged tissues may require substantially higher levels of nutrients and cofactors to support the maximum degree of recovery. Although there are no specific data, appropriate nutrition and supplementation of vitamins and trace minerals are likely to be important components in the treatment of all oncology-related neuromuscular disorders.

We do not specifically discuss any alternative or complementary therapeutic approaches because there is inadequate evidence to support the use of any of these particular treatments in this set of disorders. However, the use of these treatments continues to increase and must be included when reviewing the care of all patients with oncologyrelated neuromuscular disease (1).

SPECIFIC NEUROMUSCULAR DISORDERS

Neuropathy

Neuropathy is the most frequently encountered neuromuscular complication of cancer. Although neurotoxic chemotherapy is most commonly implicated, neuropathy also may be caused by direct or metastatic tumor infiltration of nerve or by remote (paraneoplastic) effects of the cancer. Nerve involvement may be focal or widespread, and, consequently, symptoms and signs may be focal or diffuse. Reflexes are generally reduced or absent in the affected areas. Dysesthetic pain and burning are frequent complaints. Fatigue and muscle cramps also may be troublesome.

It is useful to categorize neuropathies according to the primary neurological modalities affected: sensory, motor, or sensorimotor. The neuropathy may be further classified according to the predominant pathology: axonal loss, demyelination, or neuron cell body death. Disorders that affect sensation or strength exclusively most often are caused by lesions of the dorsal root ganglion cells or anterior horn cells, respectively, and thus are described most accurately as neuronopathies. Although one deficit may predominate, sensation and strength are usually both involved to some degree in most neuropathies.

The evaluation of a neuropathy usually involves an electromyogram (EMG) and nerve conduction studies. These tests confirm the extent and distribution of nerve involvement and help differentiate primary neuronal or axonal injury from injury to the myelin sheathe. Nerve biopsy is rarely indicated but can be helpful in differentiating direct tumor invasion (possibly amenable to chemotherapy or radiation) from a toxic or paraneoplastic process. Advances in magnetic resonance imaging (MRI) make it useful for diagnosing carcinomatous meningitis. This diagnosis cannot be excluded without a lumbar puncture. Cerebrospinal fluid (CSF) surrounds nerve roots, and examination of this fluid may clarify pathology at this level. It may also be important to evaluate potential nonneoplastic causes of neuropathy. A useful scheme for evaluation of neuropathy has been presented by Brown (2).

The primary treatment of a neuropathy, if any, is generally directed at the specific, underlying cause. The treatment of neuropathy-related symptoms depends primarily on the predominant symptom (e.g., weakness, sensory loss, pain) and is discussed in the section Symptomatic Treatments.

Chemotherapy Toxicity

Chemotherapeutic agents are among the most frequently encountered causes of neuropathy in cancer patients. A wide variety of chemotherapeutic agents has been associated with the development of neuropathy; vinca alkaloids, platinumbased agents, and taxanes are most frequently involved. Other neurotoxic drugs include misonidazole, procarbazine hydrochloride, suramin, cytozine arabinoside (ARA-C), etoposide, ifosfamide, dolostatin-10, and thalidomide (3,4,5,6,7,8,9,10 and 11).

Vinca alkaloids, such as vincristine sulfate, vinblastine sulfate, and vinorelbine tartrate, are a frequent cause of chemotherapy-induced neurotoxicity. Vincristine sulfate uniformly causes a peripheral neuropathy when used at the usual weekly doses of 1.4 mg/m^{2}or greater (12). The first clinical sign is usually the loss of ankle reflexes. Paresthesias may first become noticeable in the fingers. Although mild sensory loss does not warrant a reduction in dosage, weakness may develop rapidly, and is a dose-limiting side effect when severe. Signs of impending motor involvement include cramps and mild clumsiness. Weakness typically reverses when the dose is reduced or the drug is stopped; parasthesias take longer to disappear, and mild sensory deficits may persist. Occasionally, patients develop prolonged or permanent dysfunction. Electrodiagnostic studies demonstrate a sensorimotor polyneuropathy with predominant axonal involvement. Peripheral neuropathy may occur less frequently with vinorelbine tartrate than with other vinca alkaloids (13,14).

Cisplatin may begin to cause neurotoxicity or ototoxicity at a cumulative dose of approximately 300 mg/m^2, and more than 50% of patients who receive 600 mg/m^{2}develop symptoms (15,16). The neuropathy is predominantly sensory; decreases in vibratory, light touch, and pinprick sensation are accompanied by progressive loss of deep tendon reflexes. The loss of proprioception may result in a sensory ataxia. Despite discontinuation of the drug, neuropathic symptoms may continue to increase for weeks before stabilizing, in a phenomenon known as “coasting.” Recovery occurs over months, but is often incomplete (17). Weakness is rare in all but the most severely affected patients. Other platinum-based agents cause similar symptoms, although newer derivatives, such as oxaliplatin, may have fewer neurotoxic effects (18).

Paclitaxel and the other taxanes cause a predominantly large fiber sensory polyneuropathy. Pain, tingling, and numbness may begin within 1–3 days after a single highdose treatment (19). Weakness occasionally develops but invariably improves when the drug is discontinued. Neurotoxicity is generally not dose limiting. Risk factors for the development of neuropathy include a prior neuropathy, high doses (>250 mg/m^2), length of treatment, and possibly older age (20).

Patients who may have chemotherapy-related neuropathy should undergo a standard neuropathy evaluation to ensure that there is no other contributing cause. It is occasionally useful to follow electrodiagnostic markers of nerve dysfunction prospectively to identify impending nerve dysfunction early in the course of chemotherapy. Somatosensory-evoked responses are generally affected first, followed by a reduction in sensory amplitudes on nerve conduction studies (21).

Treatment consists mainly of limiting the patient's exposure to the offending medication. Chemoprotective agents are under investigation and ultimately may allow prophylactic therapy for neurotoxicity. Amifostine (WR-2721), for example, has demonstrated protective effects against the development of neuropathy in patients treated with cisplatin. The dephosphorylated metabolite of this compound, WR-1065, is thought to protect cells from injury by binding platinum and alkylating agents, scavenging oxygen free radicals, and repairing cell damage through hydrogen donation (22). The antioxidant glutathione also has been observed to have a slight effect in reducing neuropathy from cisplatin (23).

Cancer-Related Neuropathies

A large number of acute and chronic sensorimotor neuropathies has been associated with cancer itself. In most cases, the pathological mechanism or mechanisms are not known. The syndromes are grouped according to the predominant pathological process.

Axonal Sensorimotor Neuropathy

Polyneuropathy

Patients with advanced malignancy often develop a mild sensorimotor neuropathy, which is of little clinical importance. Much less frequently, a clinically significant axonal sensorimotor neuropathy accompanies or even precedes the diagnosis of cancer. This neuropathy typically presents with numbness and tingling in the feet. The lesion may progress to cause more widespread sensory disturbances as well as distal leg and hand weakness. Nerve conduction studies confirm an axonal neuropathy; CSF protein may be normal or, rarely, slightly elevated. The pathogenesis of this neuropathy is unknown in most cases. In some patients with non-Hodgkin's lymphoma, a lymphomatous infiltration of nerve roots and nerves has been detected on nerve biopsy; these patients may respond to antineoplastic treatment (24,25,26 and 27).

Focal Neuropathy

Isolated mononeuropathies also may develop in patients with cancer. Peroneal neuropathies at the fibular head typically develop in bedbound patients with weight loss. Loss of the usual fatty cushion predisposes the peroneal nerve to compression at this site. Nutritional, metabolic, and microcirculatory factors also may contribute to this neuropathy. Focal compression neuropathies generally improve with simple measures, such as careful positioning to avoid further compression and padding of vulnerable areas such as the elbow and fibular head (28).

Other focal neuropathies arise when malignant cells invade the nerves and cause axonal degeneration. Widespread metastatic infiltration of nerves by lymphoma or melanoma may result in a multifocal neuropathy that is indistinguishable from a sensorimotor polyneuropathy (29). If no other cause is found, contrast-enhanced MRI of the affected area maybe positive. A nerve biopsy should be considered if further antineoplastic therapy is a possibility.

Vasculitic Neuropathy

Peripheral nerves may be damaged by a cancer-associated vasculitis, which typically causes either an acute or chronic sensorimotor neuropathy, usually beginning as a painful asymmetric neuropathy or pattern consistent with a mononeuritis multiplex. Nerve conduction studies demonstrate evidence of axonal damage. The diagnosis is confirmed by the demonstration of lymphocytic infiltration and necrosis of blood vessels on nerve or muscle biopsy. Treatment with corticosteroids or other immunosuppressants may result in symptomatic improvement (30,31).

Demyelinating Neuropathy

Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barré Syndrome)

Guillain-Barré syndrome has a higher incidence in patients with Hodgkin's lymphoma and solid tumors, particularly those involving the lung. Patients suspected of having this disorder require immediate hospitalization for monitoring of their respiratory vital capacity and cardiac function. The rate of progression of this disease is highly variable; patients can deteriorate acutely in the first few days. Cancer patients appear to respond to the same therapies used for noncancer-related Guillain-Barré syndrome, such as plasmapheresis or intravenous immunoglobulin (32,33).

Chronic Inflammatory Demyelinating Neuropathy

Chronic inflammatory demyelinating disease is rarely associated with cancer (34). The pattern of weakness and sensory loss may be quite asymmetric, and nerve conduction studies reveal classic demyelinating physiology; CSF protein is frequently elevated. Remissions are reported after removal of the tumor; the neuropathy may respond to treatment with corticosteroids or intravenous immunoglobulin (26,35).

Paraproteinemic Neuropathy

A variety of neuropathies may be associated with paraproteinemia secondary to multiple myeloma, osteosclerotic myeloma, Waldenstrom macroglobulinemia, primary systemic amyloidosis, or monoclonal gammopathy of undetermined significance. Subacute or chronic axonal or demyelinating neuropathies occur in up to 13% of patients with multiple myeloma (36). In some patients with Waldenstrom macroglobulinemia or monoclonal gammopathy of undetermined significance, an IgM antibody directed against myelin-associated glycoprotein can be detected in serum and in the myelin sheath. These patients have a predominantly sensory demyelinating neuropathy (37). In most other cases, the pathogenesis of the neuropathy is uncertain, and the paraprotein may not be involved directly in the pathogenesis. A predominantly motor demyelinating neuropathy can be identified in up to 50% of patients with osteosclerotic myeloma. The neuropathy may occur as part of a syndrome consisting of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. These neuropathies may markedly improve with treatment of the tumor (38).

Patients with systemic amyloidosis due to plasma cell dyscrasia may develop a neuropathy that is predominantly sensory and typically involves small unmyelinated or thinly myelinated fibers; autonomic dysfunction is a prominent feature. The diagnosis is made by demonstration of the amyloid material on nerve biopsy. Unfortunately, this disorder has a grim prognosis; there is no effective primary treatment (39).

Neuronopathy

Paraneoplastic processes preferentially attack nerve cell bodies. The cell bodies of motor and sensory neurons are found in the anterior horn of the spinal cord and the dorsal root ganglion, respectively. Damage to the cell bodies of these neurons produces a lesion that is most accurately called a *neuronopathy*. Patients presenting with exclusively sensory or motor dysfunction should be evaluated for the presence of neuronopathy. Symptomatic therapy again depends on the predominant symptoms and is discussed in the section Symptomatic Treatments.

Motor Neuronopathy

Three separate conditions are currently best understood as motor syndromes due to a remote effect of cancer. Treatment of the tumor is of uncertain benefit; there is no effective primary therapy. Physical and occupational therapy can maximize patients' functional capabilities.

Subacute Motor Neuronopathy

Subacute motor neuropathy, which presents with slowly progressive, painless weakness (predominantly in the legs), is a well-established remote effect of non-Hodgkin's and Hodgkin's lymphomas (40,41 and 42). Bulbar involvement and upper motor neuron signs are not seen. The symptoms often develop after radiation, or when the lymphoma is in remission. After a period of progression, symptoms may improve slowly over months to years. Electrodiagnostic studies demonstrate widespread denervation. The cause of the subacute motor neuronopathy is uncertain.

Paraneoplastic Encephalomyelitis

Motor neuron involvement is also seen as a feature of paraneoplastic encephalomyelitis, which typically is associated with a sensory neuronopathy, but neurons at any level of the nervous system, including the motor neurons of the anterior horn, may be affected. When paraneoplastic encephalomyelitis is caused by small cell lung cancer, an antineuronal antibody associated with cancer, known as *anti-Hu*, is typically present.

Amyotrophic Lateral Sclerosis

Rarely is amyotrophic lateral sclerosis (ALS) related to a neoplasm. Although large, epidemiological studies generally conclude that the incidence of cancer is not increased in patients with ALS, case reports have described cancer patients with typical ALS who improved after removal of the tumor (43,44). Most patients with typical ALS do not need an evaluation for malignancy. Only patients who do not fit the typical age profile or patients with sensory complaints or other evidence of more widespread nervous system involvement should be considered for a search for an underlying occult malignancy.

Sensory Neuronopathy

So-called *subacute sensory neuronopathy*, often referred to as a *sensory neuropathy*, is the most widely recognized neuromuscular paraneoplastic syndrome (45,46). Patients typically present with numbness, dysesthesias, parasthesias, and occasionally, aching pain. The findings can be asymmetric. A sensory ataxia due to loss of proprioception is typical and can be severe. Electrodiagnostic studies show markedly decreased or absent sensory nerve action potentials, findings consistent with damage to dorsal root ganglia. Motor nerve conduction studies should be normal.

Patients who develop sensory neuronopathy without a known cancer require a detailed and perhaps repeated search for an underlying malignancy. Small cell lung cancer is by far the most commonly associated cancer; breast, ovarian, uterine, and gastrointestinal carcinomas also must be considered. The presence of anti-Hu antibodies is highly suggestive of the presence of a small cell lung cancer. In approximately 70% of patients with an anti-Hu antibody, there is evidence of CNS or lower motor neuron involvement as well (47). In these patients, an immune mechanism has been supported by the identification of a complement-binding IgG antibody that binds to an antigen found in the tumor and a 35–38-kD brain nuclear protein (48,49). Treatment of the underlying tumor may result in stabilization of the sensory neuronopathy or, in rare cases, improvement. Some patients can learn to adapt to the sensory ataxia by using visual cues, but in severe cases, function is permanently lost and patients become wheelchair bound. Intravenous immunoglobulin and plasmapheresis have not been demonstrated to be efficacious in the few reported clinical trials.

Radiculopathies

Radiculopathy implies dysfunction of the nerve roots. New onset of radicular symptoms in a cancer patient should prompt an urgent evaluation of the spinal column. Perispinal tumor masses can cause acute and rapid spinal cord compression leading to paraplegia. Tumors originating from the spinal column commonly compress nerve roots as well as the spinal cord. Pain is usually the first symptom of compressive radiculopathy. Symptoms and signs of sensory or motor dysfunction may follow, depending on the nerve roots involved and the progression of the lesion.

Radiculopathy also may be caused by leptomeningeal tumor; meningeal carcinomatosis or lymphoma can cause radicular pain, sensory loss, weakness, and areflexia. Signs of meningeal irritation, such as meningismus and, occasionally, headache, may be present. Leptomeningeal spread is most common with cancers of the breast, lung, and gastrointestinal tract, melanoma, and lymphoma, but it is possible with any tumor. Tumor-invading multiple roots can produce a polyradiculopathy that closely resembles a severe sensorimotor polyneuropathy. Cranial polyneuropathies, resulting from invasion of the cranial nerves as they traverse the subarachnoid space, are common.

Advances in MRI technology are making it the initial step in the evaluation of a patient with suspected meningeal carcinomatosis or lymphomatosis. Contrast-enhanced MRI may demonstrate enhancement of thickened nerve roots, particularly when the cauda equina is affected. If an MRI is contraindicated, myelography sometimes

demonstrates multiple nodular defects on nerve roots. Unless the MRI is unequivocally positive, the next step should be a spinal fluid examination. In nearly all cases of meningeal carcinomatosis or lymphomatosis, the spinal fluid proves to be abnormal. Spinal fluid cytology may provide a specific diagnosis, but repeated sampling may be required. In one study, 50% of patients had false-negative CSF cytology at the initial lumbar puncture, but the CSF almost always had some abnormality (50). Most experts suggest performing at least three lumbar punctures separated by several days, if initial cytologies are negative (51). Electrodiagnostic studies can confirm a radiculopathy and are also helpful in identifying a confounding or coexisting peripheral neuropathy. Rarely, a meningeal or nerve root biopsy is needed if a high degree of suspicion remains despite an unrevealing noninvasive evaluation. Meningeal tumors can sometimes be controlled for a time with radiation and intrathecal or intracerebroventricular chemotherapy; however, long-term prognosis is grim (52).

Plexopathies

The diagnosis of plexopathy in the cancer patient is perhaps the most challenging neuromuscular complication. Because of the proximity of the brachial and lumbar plexus to frequently used radiation ports, plexopathy may be a complication of radiation therapy. Differentiating between recurrent cancer and radiation-induced plexopathy can be difficult, and has obvious implications for therapy. As with all peripheral nerve injury, plexopathies usually present with both positive (e.g., tingling) and negative (e.g., numb ness) sensory complaints and weakness of the involved limb. In general, malignant plexopathy is more painful than radiation-induced plexopathy. A severely painful plexopathy is likely to be tumor-related, but radiographic or tissue diagnosis is strongly recommended before proceeding with additional antitumor therapy.

Other causes of plexopathy are rare. Idiopathic brachial plexopathy has been reported in patients with Hodgkin's disease (53). Brachial plexopathy can complicate a lymphedematous shoulder, and lumbosacral plexopathy can occur after psoas muscle hemorrhage or abscess (54,55). Regional intraarterial infusion of chemotherapeutic agents has produced local neurotoxicity manifesting as brachial or lumbosacral plexopathies (56).

Diagnostic studies are required to confirm the diagnosis. Electromyographic data can help localize the lesion and, in some cases, suggest an etiology. Radiation-induced plexopathy tends to be associated with a more diffuse injury on EMG, and with myokymia (rhythmic, repetitive spontaneous discharges). Myokymia occurs frequently in patients with radiation-induced plexopathy but has not been reported in those with malignant plexopathy (57,58). MRI may reveal a mass in the region of the plexus or enhancement along the nerve trunks. Occasionally, the etiology of a plexopathy cannot be established noninvasively, and exploration of the plexus with biopsy is required (59,60).

The treatment of a plexopathy is difficult. In patients with malignant plexopathy, radiotherapy may provide pain relief. Neurological signs may not improve, however, and pain can persist and become a difficult management problem. Radiation-induced plexopathy is generally less painful but is slowly progressive and eventually causes significant disability. There is no specific primary treatment.

Brachial Plexopathies

Brachial plexopathies are typically unilateral. The most common causes are local extension or metastatic spread of breast or lung cancer (61,62). Lymphoma, sarcoma, melanoma, and other types of cancer less commonly invade the brachial plexus. Patients with malignant brachial plexopathy typically experience pain that radiates from the shoulder girdle into the medial arm and hand (61,63). The lower nerve trunk of the brachial plexus is usually most involved, producing hand weakness, atrophy, and sensory disturbances that may mimic an ulnar neuropathy. Horner syndrome is seen in up to 50% of patients. Exacerbation of lymphedema of the arm is seen occasionally.

Radiation may induce a brachial plexopathy when given at a dose greater than 6000 cGy. Brachial plexopathy is a late manifestation of radiation therapy, and onset has been reported from 3 months to 26 years after treatment. Unlike neoplastic plexopathies, parasthesias and swelling of the arm predominate over pain. Also, the upper nerve trunk or entire brachial plexus is more likely to be involved.

For brachial plexopathy, clinical features that can help distinguish malignant from radiation-induced plexopathy are pain severity (worse with neoplasm), presence of Horner's syndrome (with neoplasm), lymphedema (uncommon after radiation), and the distribution of the arm weakness (proximal with radiation injury, and more distal from neoplastic invasion). A painful lower nerve trunk lesion with Horner's syndrome suggests a metastatic plexopathy, whereas a painless upper nerve trunk lesion with a swollen arm is more typically a sign of a radiation plexopathy (61).

Lumbosacral Plexopathies

Lumbosacral plexopathies are most commonly caused by direct extension of intraabdominal neoplasms, such as colorectal or cervical cancer, or by radiation (64,65). Pain is a frequent early feature, and the upper, lower, or entire nerve plexus can be affected. The plexopathy is frequently slowly progressive, and bilateral symptoms may be seen. Computed tomography or MRI scanning of the region of the lumbosacral plexus typically demonstrates the responsible mass. A biopsy is required only if there is no previous tissue diagnosis.

Radiation-induced lumbosacral plexopathy generally presents as slowly progressive weakness; pain occurs in 50% of patients. Like radiation-induced brachial plexopathy, the plexopathy may follow radiation by months to years. Myokymia is seen on electrodiagnostic studies in 50% of patients.

Neuromuscular Junction Disorders

Myasthenia gravis and the Lambert-Eaton myasthenic syndrome (LEMS) are the two most frequently encountered disorders of neuromuscular transmission. Myasthenia gravis may be associated with thymoma but probably is not associated with extrathymic tumors.

Although LEMS is rare, it is associated with cancer in 50–70% of patients. Among these patients with cancerassociated LEMS, 80% have a small cell lung cancer. There have been case reports of associations between LEMS and many other types of cancer, but these associations may be incidental. In patients younger than 40 years of age, the syndrome is more likely to be autoimmune than paraneoplastic; LEMS occurs more frequently in men than in women (approximately a 2:1 ratio), and cancer is the cause more often in men (70%) than women (25%) (66).

The cause of LEMS is IgG antibodies directed against the voltage-sensitive calcium channels of the motor and autonomic nerve terminals. The antibodies interfere with the voltage-dependent release of neurotransmittter at the neuromuscular junction and in autonomic nerves. Calcium channel antibody titers can be measured in the serum of LEMS patients. The immunologic stimulus is likely the voltage sensitive calcium channel of the carcinoma cells.

Proximal muscle weakness in patients with LEMS is typical, and there may be mild myalgias and tenderness of the muscles. Given these findings, LEMS can be misdiagnosed as polymyositis. Bulbar and ocular muscles are rarely affected and never to the degree seen in myasthenia gravis. Patients may complain of severe fatigue and weakness, but on examination often have only mild demonstrable weakness. Occasionally, strength may improve after exercise but then decline further with sustained activity. Deep tendon reflexes tend to be reduced or absent at rest but may increase if tested immediately after a brief, strong contraction of the appropriate muscle. Most patients complain of dry mouth, and some patients have other autonomic manifestations, including impotence, hypotension, and constipation.

The diagnosis of LEMS can be confirmed through electrodiagnostic studies. Routine nerve conduction studies often show reduced motor amplitudes due to impaired release of acetylcholine. A small decrement is seen with repetitive stimulation at low rates; however, with high rates of stimulation or immediately after a brief contraction of the muscle, the motor amplitudes markedly increase to at least double their resting size (most likely because of an increase in the concentration of calcium in the nerve terminals leading to increased acetylcholine release). In questionable situations, the diagnosis can be confirmed with single-fiber EMG (67).

Therapy for LEMS should be tailored to the individual patient and based on clinical severity, the presence of underlying disease, and life expectancy. If the diagnosis of LEMS has been confirmed in a patient without a known malignancy, an extensive search for malignancy must be carried out. Computed tomography scanning of the chest and sometimes bronchoscopy are recommended. If small cell lung cancer is identified, initial therapy should aim at treating the cancer. Weakness associated with LEMS frequently improves with effective cancer therapy, and often, no further treatment is needed (68,69). Cholinesterase inhibitors, such as pyridostigmine, usually do not produce significant improvement, but in rare patients there is some benefit. Pyridostigmine bromide can be tried at a dose of 30–120 mg every 4–6 hours if required. Immunotherapy with plasma exchange, intravenous immunoglobulin, corticosteroids, or azathioprine may be used if the weakness is severe and unresponsive to less aggressive therapy. The orphan drug 3-4 diaminopyridine improves strength and lessens autonomic symptoms in most patients with LEMS (70).

As with myasthenia gravis, drugs that adversely affect neuromuscular transmission should be avoided. These include the aminoglycosides, beta-blockers, calcium channel blockers, and antiarrhythmics such as quinine sulfate, quinidine sulfate, or procainamide hydrochloride. Neuromuscular blocking agents typically used during intubation have an exaggerated and prolonged effect in patients with LEMS.

Myopathy

Except for the local invasion of myofascial structures, primary muscle dysfunction associated with cancer most often arises as a remote effect, thought to be due to autoimmune or toxic metabolites. The best known example is dermatomyositis. Some cancer therapies, particularly corticosteroids, also can cause a myopathy. Myopathy should be suspected in the patient with progressive weakness, especially if proximal, and no sensory symptoms. Most myopathies are associated with an elevated creatinine phosphokinase. Myopathy often can be confirmed by EMG, and a muscle biopsy may help to define the syndrome fully. Treatment usually involves therapy directed towards the specific underlying disorder. There are few symptomatic therapies.

Inflammatory Myopathies

Historically, there has been considerable confusion regarding the relationship between cancer and the inflammatory myopathies. Whereas some studies have demonstrated an increased incidence of neoplasm in patients with both polymyositis and dermatomyositis, others found no such relationship. Currently, little evidence suggests that either inclusion-body myositis or polymyositis is associated with cancer; however, there does appear to be an increased incidence of malignancy in patients with dermatomyositis, particularly among older patients. In a recent series, approximately 25% of patients with dermatomyositis had a known malignancy at presentation, or a malignancy was detected soon after the diagnosis of dermatomyositis (71).

The distinction between polymyositis and dermatomyositis is based on the presence or absence of the characteristic skin manifestations of dermatomyositis. These include a purplish (heliotrope) periorbital rash and a more widespread erythematous pruritic scaly rash over extensor surfaces and sun-exposed areas.

Dermatomyositis associated with malignancy usually responds to immunosuppressive therapy with oral corticosteroids, such as prednisone at 40–60 mg per day for at least 1–2 months, followed by a slow taper. The daily dose can be reduced by 5 mg every week until 30 mg per day, with further tapering at only 2.5 mg per week. Relapse frequently occurs after early or rapid reduction in steroid doses. Other immunosuppressive agents, including methotrexate, cyclophosphamide, chlorambucil, and azathiaprine, have been used, most typically in patients who do not respond to corticosteroids or cannot tolerate their side effects. Intravenous immunoglobulin at a total dose of 2 g/ kg divided over several days also was recently demonstrated to be effective (72). Treatment of the underlying tumor also may result in improvement of the myositis (73).

Cancer-Related Muscle Necrosis

Cancer-related muscle necrosis, a rare, rapidly progressive, fatal muscle degeneration, has been linked to small cell lung cancer and to gastrointestinal, breast, and bladder cancers (74). This disorder presents with a rapidly progressive weakness that spreads from the limbs to involve bulbar and respiratory muscles. Electrodiagnostic studies demonstrate changes typical of myopathy. On muscle biopsy, there is profound muscle-fiber necrosis with little or no inflammation. In general, no treatment has proved helpful.

Carcinoid Tumor–Associated Myopathy

Carcinoid tumors may cause muscle damage and progressive proximal weakness, perhaps related to secretion of serotonin or other substances by the tumor (75). Most histopathologic changes are nonspecific, with preponderance of type I fibers and type II fiber atrophy. The symptoms sometimes improve with a serotonin antagonist such as cyproheptadine hydrochloride or methysergide.

Steroid-Induced Myopathy

Corticosteroids often produce myopathy, which can be progressive. The weakness typically has an insidious onset, but may occasionally be sudden. Despite profound weakness, the serum creatinine phosphokinase is typically normal or only mildly elevated, and EMG may or may not reveal myopathic changes. Muscle biopsy may demonstrate the nonspecific finding of type II muscle fiber atrophy. Necrosis and regenerating fibers are rarely seen. Susceptibility to steroid myopathy varies widely. Patients who develop significant cushingoid body habitus seem to be more at risk (76). The fluorinated corticosteroids, such as dexamethasone, betamethasone, or triamcinolone, more often are implicated in the development of steroid myopathy.

Patients often improve with a reduction in the steroid dose. Strength in some patients who are receiving a fluorinated drug improves if therapy is changed to a nonfluorinated steroid, such as prednisone or hydrocortisone. Physical exercise also can help prevent muscle weakness and atrophy.

SYMPTOMATIC TREATMENTS

Primary treatment of the oncologic or neuromuscular lesion should be provided if feasible and appropriate for the patient's medical condition and goals. In some cases, this strategy may halt or reverse neurological deficits and possibly provide some degree of symptom control. Purely symptomatic therapies are often needed as well, and become the major interventions for those who cannot benefit from primary therapy.

Pharmacological

Aside from muscular cramps, symptoms involving the peripheral nervous system are predominantly neuropathic in origin, specifically sensory loss, paresthesias, dysesthesias, or nondysesthetic pain. Pain is usually the most compelling symptom, and management can be challenging. Opioid drugs, combined with nonopioid analgesics and adjuvant analgesic drugs, are commonly administered. The adjuvant analgesics are particularly important in the treatment of neuropathic pain, which overall is less responsive to the opioids than other types of pain.

Occasional patients with medically refractory pain may be candidates for an anesthetic, neurostimulatory, or neurosurgical intervention. The decision to undertake an invasive therapy must carefully consider potential risks and benefits and relies on a comprehensive assessment of the patient.

Muscle cramps can be particularly troublesome in patients with cancer. Although cramps are often thought of as nonspecific, in reality they typically point to underlying neuromuscular or metabolic dysfunction. In a recent study of 50 cancer patients who complained of muscle cramps, examination and evaluation of the patient led to a specific etiology in 82% (77). Peripheral neuropathy was identified in 22 of the patients, nerve root or plexus lesions in 17 patients, and polymyositis in two patients. Hypomagnesemia was thought to account for muscle cramps in one patient. Thus, muscle cramps typically mark the presence of an identifiable and often previously unsuspected neurological disorder.

Cramps are most effectively eliminated by treating the underlying cause. Unfortunately, this is rarely possible in patients with cancer, except when cramps are due to calcium abnormalities. Cramps occasionally may be successfully treated using agents thought to stabilize muscle membrane, such as quinine sulfate, or a number of antiepileptic medications. Quinine sulfate appears to be most effective in treating nocturnal cramps, whereas antiepileptic medication should be tried for daytime cramping. Strict attention to adequate hydration and electrolyte balance are also critical. Other agents, such as benzodiazepines, antispasticity drugs (e.g., baclofen, tizanidine hydrochloride), antiinflammatory agents, or narcotics, have not been shown to be effective, but their sedating properties may help patients sleep more readily.

The mainstays of pharmacological treatment for positive neuropathic symptoms (e.g., dysesthesias, paresthesias, radiating pain) are anticonvulsants and tricyclic antidepressants (78,79). Less well studied are baclofen, the benzodiazepines, oral anesthetic agents, and a-adrenergic blockers. Numbness or sensory loss does not respond to medication and can only be reduced by addressing the primary neurotoxic process and allowing injured nerves to recover.

The following important principles are generally applicable. Choose each medication carefully, considering both the intended effects and potential side effects. If potential side effects are significant, start with a very low dose, increasing slowly every few days to allow patients to become tolerant to the side effects. Increase the dose of each medication until the desired effect is achieved, until side effects become unmanageable, or until high therapeutic drug levels are obtained. Give each medication an adequate trial before considering it a failure or success, as some drugs may require several weeks to reach their maximum efficacy. Even when treating the same symptoms in different patients, it is important to remember that each patient's response to neuroactive agents is different, and a number of different agents should be tried sequentially until an effective one is found.

Six new anticonvulsants have been introduced in the last 5 years, several of which have better safety profiles than those of existing medications. The introduction of these new drugs has resulted in increased treatment options for neuropathic pain. Currently, gabapentin has become the drug of first choice because of its low side-effect profile and relative lack of interaction with other medications. Two excellent, doubleblind, randomized, placebo-controlled clinical trials have been conducted

showing efficacy and safety (80,81). Based on the information currently available, a number of the newer agents also show similar promise (82,83 and 84).

Rehabilitation

Rehabilitation should play an important role in the treatment of any neuromuscular complication of cancer. There is increasing evidence that monitored exercise can improve muscle strength and endurance while reducing the complications of joint contractures, disuse atrophy, joint stiffness, osteoporosis, and pain. In a study of 301 terminal cancer patients, an increase in the Barthel mobility index from 12 to 19 was achieved with a supervised program of rehabilitation in the hospice setting. The rehabilitation program was thought to be effective by most patients and their families. In another study, a supervised program of active resistance and endurance exercise was shown to maintain and even increase muscular strength in patients with neuromuscular disease (85). Although the special features of neuromuscular disease in cancer patients were not addressed specifically in these studies, it is reasonable to conclude that supervised rehabilitation efforts, particularly physical therapy, can be effective in maximizing the function of patients suffering from neuromuscular complications of cancer.

Over time, weakness can lead to contractures of the affected joint. Regular stretching exercises may prevent this complication. For patients with severe weakness from any cause, splinting in a neutral position also may be needed to prevent contractures. In addition to exercise, appropriate devices can increase patient function. Orthotic braces may allow a weak joint to function more normally. For example, molded ankle-foot orthotics, which stabilize the ankle in a neutral position and eliminate foot drop, can help a patient maintain ambulation.

Significant loss of proprioception often results in gait instability. A cane or walker can provide additional stability, which often helps patients feel more secure. Walking should be encouraged, because gait tends to improve as the brain adapts to a reduced level of proprioceptive input. Use of a cane, walker, or even wheelchair should be encouraged to allow continued independence. Reduced sensation in the hands produces difficulty with fine manipulation, such as buttoning a shirt. Special devices can be created to improve hand and finger function. A trained occupational therapist is best qualified to evaluate and fit patients for such assistive devices.

Other techniques that may be of use for pain or other neuromuscular symptoms include heat, cold, massage, transcutaneous electrical nerve stimulation, and acupuncture (86,87,88,89 and 90). The available literature is generally inconclusive about the efficacy of these therapies; trials were recommended by a recent expert panel (91).

Psychological

Cognitive interventions, such as relaxation, imagery distraction, reframing, hypnosis, and biofeedback, can be helpful in managing pain and improving function (92,93,94,95 and 96). Because the success of these techniques is highly dependent on the patient's ongoing commitment to use them, the clinician must try to identify techniques that are best suited for a patient's specific needs and personality.

SUMMARY

Through a logical approach guided by the physical examination and selected additional studies, the etiology of most neuromuscular complications of cancer can be determined. In many cases, therapy aimed at the specific etiology is effective. Symptomatic therapies should always be considered to enhance function and reduce discomfort. Although many of the neuromuscular manifestations of cancer lack effective primary therapy, significant palliation should be possible in most patients.

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39

DELIRIUM

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Delirium has been defined as a transient organic brain syndrome characterized by the acute onset of disordered attention and cognition and accompanied by disturbances of psychomotor behavior and perception (1). It is highly prevalent in the medically ill and has been associated with a wide range of etiological factors. Given data from studies in other medical populations (2,3), it is likely that delirium is under-recognized by medical and nursing staff in the oncology setting. Unless promptly reversed, this condition can increase family distress and precipitate conflict between staff and families (4). The presence of delirium has been shown to prolong hospital stay and increase mortality (5,6). Those caring for oncology patients must be cognizant of the prevalence and phenomenology of delirium and be able to initiate and monitor appropriate treatment interventions.

TERMINOLOGY

The study of mental status changes in patients with cancer and other illnesses has been hampered by a lack of consistency in terminology. A plethora of terms have been used to describe the clinical syndrome consistent with delirium. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV*) of the American Psychiatric Association (7) provides the current gold standard for syndrome definition in psychiatry. This document provides the definition that is used throughout this chapter. Delirium is considered to be a single nosologic entity (8), and the *DSM-IV* proposes specific diagnostic criteria for its diagnosis (Table 39-1) (7). Although the earlier *DSM-III-R* criteria classified delirium as one of the organic brain syndromes (9), this classification was seen to imply that other psychiatric illnesses had no biological correlates. To correct this apparent anomaly, the term “organic brain syndromes” was revised in the *DSM-IV*, which classifies delirium in the category titled “Delirium, Dementia and Amnestic and Other Cognitive Disorders” (7).

A. Disturbance of consciousness with reduced ability to focus, sustain and shift attention.
B. Change in cognition (e.g., memory deficit, disorientation, language disturbances) or perception disturbances not better explained by a preexisting stabilized or evolving dementia.
C. The disturbance develops over a short period of time and tends to fluctuate during the course of the day.
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

TABLE 39-1. CRITERIA FOR DIAGNOSING DELIRIUM DUE TO A GENERAL MEDICAL CONDITION: *DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, FOURTH EDITION*

The diagnostic criteria for delirium have evolved over time, yet the term *delirium* is frequently used without adherence to these criteria. In the past, for example, delirium has been used to describe conditions linked to febrile states characterized by agitation and associated with perceptual abnormalities, clouding of consciousness, and disorientation (10). In addition, other terms, particularly “confusion” and “encephalopathy,” have been widely used in the clinical setting to describe the mental status changes that would fulfill the criteria for delirium. The French literature described the phenomena found in these states as “oneirism” or “oneiric consciousness,” with the most striking case of a confused oneiric state being delirium tremens (DT) due to alcohol withdrawal.

The terms “encephalopathy” and “acute confusional state” have been used by neurologists to describe acute changes in mental status (11,12). These terms are applied in lieu of the psychiatric classification based on the *DSM* criteria. As a consequence, a dichotomous tendency exists between the psychiatric and neurological literature. This dualism is usually only semantic. The *DSM* classification criteria are preferred because they have the advantage of defining the essential features of the syndrome (see the section Mental Status Changes and Clinical Applications of Diagnostic Criteria) while leaving open the door to further classifying clinical and patho-physiological subtypes. In the clinical setting, the imprecise terminology has been compounded by a lack of understanding of the important distinction between symptoms and pathological processes or diagnoses. Symptoms are subjective “physical or mental phenomena . . . accompanying a disorder and constituting evidence for it” (13). When used to describe a subjective experience, “confusion” is a symptom. When used by medical and nursing staff to describe a patient's mental state, however, the term is a broad descriptor that is neither a symptom nor a diagnosis. It should never be used synonymously with the diagnosis of delirium. “Confusion” has no diagnostic specificity and may characterize numerous disease states, including both delirium and dementia. Given evidence of confusion, a clinician should consider a detailed clinical examination to facilitate a diagnosis for the mental status change and to seek out etiological factors.

The problems with inconsistent terminology that have characterized both the study of delirium and its diagnosis in the clinical setting may be minimized by the use of *DSM* criteria. Instruments have been developed based on these criteria that facilitate the diagnosis and allow the monitoring of the syndrome (see the section Evaluation Instruments for the Assessment of Delirium). As further research efforts are directed to delirium, it may be that the diagnostic criteria will be further refined. Although the *DSM* criteria for delirium are now considered the gold standard for diagnosis, these criteria and the *DSM-IV*–classified disorders are reflections of a consensus of the formulations of current knowledge in psychiatry. This is an evolving field, and the classification is likely to evolve further and indeed may, as it exists now, not encompass all conditions that may be legitimate targets for treatment or research.

PATHOPHYSIOLOGY OF DELIRIUM

Delirium is an altered mental state characterized by altered alertness and impaired cognition that has been described by Engels and Romano as a syndrome of cerebral insufficiency (14). It is considered to be a stereotyped response of the brain to a spectrum of differing insults and has been viewed as a state on the continuum between normal wakefulness and stupor and coma. The number of possible etiologies, including head trauma, metabolic abnormalities, and innumerable drugs, suggests the existence of a final common pathway with diverse inciting pathophysiologies. An alternative interpretation is that each of the clinical subtypes of delirium is a final common pathway for a set of etiologies or pathophysiologies that share characteristics. The current state of knowledge regarding the pathogenesis of delirium has been most comprehensively reviewed by Trzepacz (15,16).

Anatomically, it is known that both subcortical and cortical structures are important in the development of the syndrome (15,16). Any pathological process that, either structurally or functionally, affects most or all of the cortical mantle may modify the level of consciousness (12). This mechanism of diffuse damage or dysfunction is

likely to play a part in the pathophysiology of many cases, particularly in delirium triggered by metabolic dysfunction.

Some specific brain structures have also been implicated in the pathogenesis of delirium (15,16). These include the brainstem nuclei and tracts that subserve normal wakefulness and the regulation of the sleep-wake cycle (17), as well as hypothalamic-cortical pathways (18). Mesulam et al. observed that right-sided cerebral infarcts are more often associated with delirium (19). The prefrontal, orbital, and nondominant parietal regions and the thalamic and hippocampal structures are also likely to be important structures (15,16).

Abnormalities in cerebral blood flow have been described in delirium, although the etiological implications of these observations are uncertain (15,16). A reduction in cortical flow has been demonstrated in subclinical hepatic encephalopathy (20) and in posttraumatic delirium (21). Cerebral blood flow has been reported to be globally increased in DT (22).

Many neurotransmitters have been implicated in the pathogenesis of delirium (15,16). For example, abnormalities in cholinergic neurotransmission have been implicated in the pathophysiology of many different forms of delirium. It has been postulated that a reduction of acetylcholine synthesis and release may unify many clinical observations in etiologically diverse forms of delirium (15,16). Other neurotransmitters have also been tentatively implicated in specific types of delirium (15,16). For example, overstimulation of the gamma-aminobutyric acid system has been linked to hepatic failure encephalopathy and benzodiazepine intoxication; gamma-aminobutyric acid system understimulation may relate to benzodiazepine and alcohol withdrawal; *N*-methyl-D-aspartate receptor blockade could be involved in phencyclidine delirium; serotonin antagonism could be a causal factor in D-lysergic acid diethylamide hallucinations and delirium; and dopaminergic overactivity has been considered a cause of hyperactive deliria (15,16).

These diverse associations further suggest the existence of a final common metabolic and cellular pathway for delirium (23). Hypoglycemia, hypoxia, ischemia, and other insults may affect oxidative metabolism and induce profound changes in the cholinergic system. Such insults potentially also impact on the function of other neurotransmitters, including dopamine and glutamate. These changes may occur in association with conditions that predispose to delirium, including nutritional cofactor deficiencies (e.g., thiamine), aging processes, and disease states such as Alzheimer's disease. The link between neurotransmitter deficiency, altered brain metabolism, and the clinical manifestations of delirium is postulated to be based on abnormalities of the second messenger systems including calcium, cyclic guanosine monophosphate, and the phosphatidylinositol cascade (23).

It is clear that there is a need for a greater understanding of the pathophysiology of delirium. As such an understanding evolves, it may in time allow the development of treatment strategies aimed at specific abnormalities in second messenger systems, neurotransmitters, or other abnormalities.

ELECTROPHYSIOLOGY OF DELIRIUM

The electroencephalogram (EEG) of patients with delirium, regardless of the etiology of the delirium, demonstrates a generalized symmetric slowing of the EEG with reduction of the alpha rhythm and an increase in delta and theta frequencies (14). These changes are not dissimilar to those found in stages of the sleep pattern. In general, the degree of EEG slowing correlates with decrease in arousal. In some conditions, EEG fast wave activity, beta activity, is also present (24). This activity is more prevalent in delirium characterized by hyperactive phenomena, such as DT.

Recent studies have suggested that EEG techniques may be useful in the study of delirium, clarifying the differential diagnosis and severity and providing a better method for serial monitoring (25,26,27 and 28). EEG findings, specifically decreased alpha and increased delta and theta frequencies, have been demonstrated to correlate with low Mini-Mental State Examination scores in delirious patients (26,27). In these investigations, the reduction of alpha rhythm, demonstrated using quantitative spectral analysis techniques, was particularly useful in diagnosing delirium, whereas the pattern of theta and delta waves was more useful in differentiating dementia from delirium. The utility of EEG in the differential diagnosis of delirium has also been demonstrated in the differentiation of nonconvulsive status epilepticus from delirium and several specific diagnostic entities. For example, the EEG associated with delirium produced by high-dose ifosfamide shows rhythmic complexes typical of seizurelike activity, in contrast to generalized symmetric slowing of the EEG considered to be typical of other types of delirium (29).

Evoked potential techniques have seldom been applied to the study of delirium (15,16). Abnormalities of brainstem acoustic responses and visual evoked potentials have been observed in hepatic encephalopathy (30). Long latency evoked potentials, which are influenced by cognitive processes, can be an interesting tool for exploring the early manifestations of delirium, pattern of recovery, and therapeutic interventions. These potentials have been used in identifying subclinical encephalopathy in liver transplant candidates (30), in interleukin administration (31), and in recovery from head trauma (32).

PREVALENCE AND INCIDENCE OF DELIRIUM

In hospitalized medical and surgical patients, the prevalence of delirium is approximately 10% (10,33,34). In hospitalized cancer patients, the prevalence ranges from 8% to 40% (35,36 and 37). A higher prevalence, reaching as high as 50% in some studies, has been demonstrated in specific subpopulations, including the elderly, patients in the postoperative period, patients presenting to the emergency room, and patients in the terminal phase of illness (10,33,37,38,39,40 and 41). Although recently there have been an increasing number of studies undertaken that focus on the terminally ill population (suggesting prevalence figures of 20–88%, depending on how close to death the survey is undertaken) (37,38,42,43 and 44), studies specifically exploring the prevalence of delirium remain rare in the population with malignant disease (35).

Although small numbers of patients have been studied in the setting of terminal illness related to cancer, the incidence of delirium has been even less widely investigated than its prevalence, particularly in the oncology setting (37,38,42,45). In a review of 26 relevant and valid studies on postoperative delirium, Bitondo Dyer et al. concluded that the overall incidence was almost 36.8%, with wide variation (0.0–73.5%) (39). Similar variability in the incidence of delirium (14–56%) has been reported in hospitalized, medically ill, elderly patients (5,33,34,46). In a study by Gagnon et al., 18 (20%) of 89 cancer patients consecutively hospitalized for terminal care were positive on screening at admission, and among the 71 who were free of delirium at admission, the incidence of confirmed delirium was 32.8% (42). In a similar population, 104 patients in an acute palliative care unit in a university-affiliated teaching hospital, Lawlor et al. diagnosed delirium in 44 patients (42%), and of the remaining 60, delirium developed in 27 (45%) (43). Reversal of delirium occurred in 46 (49%) of 94 episodes in 71 patients, and terminal delirium occurred in 46 (88%) of the 52 deaths (43).

Clinical experience suggests that the risk of delirium varies during the course of a disease, including cancer. The incidence of delirium is likely to be relatively high during episodes of sepsis; postoperatively; when multiple drugs are administered, including chemotherapeutic agents, opioids, and anticholinergics; and in the terminal phases of illness. In the oncology setting, several studies have now reported on delirium and/or cognitive failure and demonstrated, with the exception of one study suggesting a lower incidence (42), that these entities developed in >80% of cancer patients nearing death (38,43,45). One study, which did not use strict criteria for diagnosis of delirium, suggested that the incidence of delirium in patients after surgery for head and neck cancer was 9–25% (47).

The reported variation in the prevalence and incidence of delirium reflects differences in the diagnostic criteria and variation in the populations studied. Although the studies cited previously specifically sought to define cases of delirium, delirium may appear to be less prevalent in the clinical setting than the reports would suggest. The most likely factor contributing to this perception is underdiagnosis. It is well documented that the symptoms of delirium are frequently attributed to other disorders or, alternatively, not observed at all (2,3,48,49). In the emergency room setting, for example, one study demonstrated that only 6% of delirium diagnoses were detected by the emergency room physician (49). In a series of elderly medical patients, the physicians' diagnoses correctly identified only eight of 47 patients as being delirious or acutely confused (3).

PREDISPOSING, PREDICTIVE, AND ETIOLOGICAL FACTORS IN DELIRIUM

The sociodemographic and disease-related factors that may predispose to delirium or predict its occurrence have not been documented in cancer patients. The studies that have investigated delirium in the oncology setting have generally sought to address the spectrum and prevalence of a range of psychiatric diagnoses rather than to address factors involved in specific diagnoses, such as delirium (35,36 and 37,44). As a consequence, the number of delirious cancer patients that has been studied has not been large enough to allow investigators to draw conclusions that relate to predictive factors.

Although there is a paucity of studies in the cancer population and further research is needed in this area, studies that have explored delirium in the hospitalized elderly and in patients before surgery may have some application in the cancer population. This is particularly so given that a high proportion of cancer patients is elderly and many undergo surgery. Unfortunately, many of the studies of delirium predictors have significant methodological limitations. In some studies, for example, standardized validated instruments were not used for delirium diagnosis. Other studies failed to distinguish baseline vulnerability and precipitating factors. Inouye and Charpentier proposed a multifactorial model for delirium in the hospitalized elderly that may be relevant in the cancer population (34,41,50). The model involves the interaction between “baseline vulnerability” and “precipitating factors or insults” (41). In this model, baseline vulnerability is defined by the predisposing factors present at the time of admission to hospital, and the precipitating factors are the noxious insults that occurred during hospitalization. Patients who have high baseline vulnerability may develop delirium with any precipitating factor, whereas those with low baseline vulnerability will be more resistant to the development of delirium, even with noxious insults. The factors that Inouye et al. specifically demonstrated to be contributory to baseline vulnerability in the elderly include visual impairment, severe illness,

cognitive impairment, and an elevated serum urea nitrogencreatinine ratio of ³18 (dehydration) (46,50). Other studies have implicated risk factors including each of the aforementioned factors; age; dementia; depression; alcohol abuse; the preoperative use of anticholinergic drugs; poor functional status; and markedly abnormal preoperative serum sodium, potassium, or glucose levels (5,39,51,52,53,54 and 55). Certain medications have also been implicated as risk factors for delirium, including neuroleptics, opioids, and anticholinergic drugs (5,52,56).

Several authors have suggested predictive models for the stratification of patients at risk for delirium (41,46,47,50,53,54). The Inouye et al. predictive model for elderly hospitalized patients is based on the four baseline vulnerability factors (discussed above) and five precipitating factors (the use of physical restraints, malnutrition, more than three medications added, use of a bladder catheter, and any iatrogenic event) (41,46,50). Although the precipitating factors may not in themselves represent the "cause" of delirium, each may reflect an array of risk factors. Such "risk" may be a consequence of the factor's direct effect on cerebral function or it may relate to the fact that the presence of the factor increases the likelihood of other delirium precipitants or risks also being present, including immobility or infection. Precipitating factors occurred during hospitalization, whereas baseline factors were present at admission to hospital. The precipitating and baseline vulnerability factors were shown to be highly interrelated and contributory to delirium development in independent, substantive, and cumulative ways (41). More recently, Inouye et al. proposed a multicomponent prevention strategy that systematically targeted any of six risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairments, hearing impairments, and dehydration (50,57). In a prospective trial involving 852 elderly patients with intervention and "usual care" arms, this group of investigators used standardized protocols to ameliorate each of these risk factors when present (50,57). The number of episodes of delirium and the total days with delirium were significantly lower in the intervention group. Once delirium developed, however, the severity and the rate of recurrence were the same in both groups of patients. This latter point serves to emphasize the importance of primary prevention in the treatment of delirium. No studies of this nature have been conducted, to date, specifically in an oncology population.

Other authors have attempted to define predictive models in the elderly and in surgical populations based, for the most part, on the admission characteristics of patients rather than on in-hospital events (41,46,47,53,54). In a study of advanced cancer patients in palliative care settings, Caraceni et al. found that the diagnosis of delirium was independently associated with male gender, central nervous system metastases, lower performance status, worse clinical prediction of survival, and progestational treatment (58). In another of the few studies undertaken in oncology patients, Weed et al. sought to define a method of preoperative identification of patients at risk for delirium after major head and neck cancer surgery (47). In this study, the defined criteria included factors related to age, alcohol abuse, cognitive impairment, biochemical abnormalities, and function. Although these may indeed be valid predictive factors, the latter study methodology did not use strict criteria for the definition of delirium.

In cancer patients, the potential etiologies of delirium, as distinct from "risk factors," may be divided into direct effects related to tumor involvement and indirect effects (Table 39-2) (59). The latter category includes drugs, electrolyte imbalance, cranial irradiation, organ failure, nutritional deficiencies, vascular complications, paraneoplastic syndromes, and many other factors (43,59,60,61,62 and 63). Two studies have looked at these factors. The first, a survey of 140 confused cancer patients referred initially for a neurology consultation demonstrated a multifactorial etiology in most cases (64,65). A single cause of the altered mental status was found in 31% of patients, whereas 69% had multiple causes; the median number of probable contributing factors in each patient was three (64). Drugs, especially opioids, were associated with altered mental status in 64% of patients, metabolic abnormalities in 53%, infection in 46%, and recent surgery in 32%. A structural brain lesion was the sole cause of encephalopathy in 15% of patients. Lateralizing neurological signs were found in 41% of patients, and of those 42% had cerebral metastases. Importantly, however, it was noted that 25% of patients without lateralizing signs who had neuroimaging had a focal cerebral lesion defined as a cause or a contributory factor to the delirium. Two-thirds of the patients in this survey recovered cognitive function when the cause of the delirium was treated. In a second study addressing this problem, Lawlor et al. studied a population of 104 patients with advanced cancer admitted to a palliative care unit (43). In this population, as in Tuma's population, the median number of precipitating factors was three, and 49% of patients had delirium that was reversible. Psychoactive medications, predominantly opioids were precipitating factors that were independently associated with reversibility of the delirium, but the authors concluded that oftentimes more than one factor (e.g., opioid medication and dehydration) requires attention if the delirium is to be reversed (43).

Primary tumors of the nervous system
Metastases to the central nervous system
Cerebral tumor
Leptomeningeal tumor
Nonmetastatic complications of cancer
Metabolic encephalopathy due to organ failure
Other metabolic disturbances
Electrolyte imbalance, including disturbances of sodium, calcium, and others
Hypoglycemia or hyperglycemia
Infection
Hematological abnormalities
Nutritional deficiencies
Paraneoplastic syndromes
Vasculitic processes
Treatment side effects from
Chemotherapeutic agents
Steroids
Radiation
Opioids
Anticholinergics
Antiemetics
Other medications

Data from Patchell RA, Posner JB. Cancer and the nervous system. and Plotkman SB, Lesko LM. Delirium and dementia. In: Holland J, Rowland J, eds. Handbook of psychooncology: psychological care of the cancer patient. New York, Oxford University Press, 1989, with permission.

TABLE 39-2. CAUSES OF DELIRIUM IN CANCER PATIENTS

Other studies have demonstrated that drug interactions and metabolic failure (especially renal impairment) can produce unexpected toxicities, especially in the patient with advanced disease (66,67 and 68). Other etiologies (Table 39-2) are also possible in cancer patients. For example, one report established delirium as a possible complication of leptomeningeal disease (69) and paraneoplastic encephalitis, including that associated with Anti-Hu and other antineuronal antibodies, has also been reported as a cause of delirium (70,71 and 72). Nonconvulsive epileptic status, which can occur in association with complex metabolic problems and also with ifosfamide encephalopathy, is a condition that can also result in altered consciousness and can lead to a clinical state of delirium (29). EEG can be used to confirm this diagnosis.

Finally, it is important to recognize that many factors contributing to delirium are potentially reversible; these are often underestimated in this population, including, among others, dehydration (73), borderline renal function, infections, metabolic causes, drug withdrawal, psychoactive medications, and the accumulation of opioid metabolites (43,64,74,75).

MENTAL STATUS CHANGES AND CLINICAL APPLICATIONS OF DIAGNOSTIC CRITERIA

Investigators have proposed two theoretical models of mental status change to explain the clinical manifesta tions of delirium. One model suggests a homogeneous deterioration of cognitive functions (10), and the other, based on the studies by Chedru and Geschwind, suggests that the cognitive deficits are secondary to attention failure (70,71 and 72,76,77 and 78). The latter theory suggests that common clinical features—distortion and disorganization of memories, orientation, thinking, and language—occur because of an abnormal attention matrix and that the cognitive performances with the highest attentional demand, including language and writing abilities, are likely to be the most affected. Although in the clinical setting disturbed attention failure is a prominent feature of the syndrome and is considered to be among the essential criteria for diagnosing delirium (Table 39-1) (7), the variety and intensity of symptoms suggest that regional areas of the brain are likely to be functioning abnormally and contributing to the clinical picture (15,16). The common clinical features of delirium are listed in Table 39-3.

Insomnia and daytime somnolence
Nightmares
Restlessness, agitation
Irritability
Distractibility
Hypersensitivity to light and sound
Anxiety
Difficulty in marshaling thoughts
Fleeting illusions, hallucinations, and delusions
Emotional lability
Attention deficits
Memory disturbances

TABLE 39-3. DELIRIUM SYMPTOMS

Several of the characteristic clinical features of delirium contribute to the tendency to underdiagnose the condition. For example, the symptoms and signs fluctuate and the diagnosis may be overlooked if careful attention is not given to the changes in mental status examination over time. Additionally, subtle changes frequently precede the onset of delirium. These minor symptoms and behavioral changes may go unnoticed, only to be recalled later in family or staff interviews. Even when the symptoms of delirium are most apparent, the fact that these symptoms are highly prevalent in advanced cancer (79,80 and 81) contributes to diagnostic confusion. A patient with cancer may, for example, be restless, anxious, depressed, irritable, angry, or emotionally labile. Clinicians must be cognizant of the fact that these symptoms are not specific for a diagnosis. The spectrum of symptoms must be assessed because in isolation each may be a manifestation of an adjustment disorder, may represent a symptom of delirium, or may be a consequence of any of a large number of conditions, including dementia (Table 39-3 and Table 39-4) (35,44,82). Finally, although most patients have disturbances in multiple aspects of cognition and behavior, the highly variable clinical manifestations of the syndrome result in significant interpatient variability.

TABLE 39-4. DIFFERENTIAL FEATURES OF DELIRIUM, DEMENTIA, AND PSYCHOSIS

In the early stages of delirium, some patients experience an isolated disturbance that may be related to an organic cause that alone may not fulfill the criteria for a diagnosis of delirium. Findings frequently include daytime somnolence with nighttime insomnia and subtle mood and personality changes (Table 39-3). For example, a patient may experience hallucinations or a mood disturbance in the absence of any other evidence of cognitive dysfunction. Such problems must be fully assessed and monitored over time. If other disturbances occur later, the criteria for a diagnosis of delirium may then be met.

Although the clinical presentation of delirium is often extremely varied, the diagnosis can be established on the basis of new-onset disturbances involving cognition, affective state, perception, or arousal and responsiveness. Table 39-1 outlines the specific *DSM-IV* criteria for diagnosis of delirium and each of these criteria must be met for diagnosis.

The first of the *DSM* diagnostic criteria for delirium relates to disturbance of consciousness and impaired attention. This disturbance can be highly variable, characterized by increased or decreased arousal or merely by distractibility and reduced responsiveness. Three clinical variants of delirium have been described based on the type of arousal disturbance: hypoalerthypoactive, hyperalert-hyperactive, and mixed type (with fluctuations from hypoalert to hyperalert) (82,83). The hypoactive form is characterized by lethargy and appears to be associated with less “positive” clinical phenomena than the hyperactive form, which is often accompanied by hallucinations, delusions, and illusions. In one study, 15% of cases presented hyperactive delirium, 19% had the hypoactive form, 52% had mixed forms, and 14% had neither (83).

Although few studies have explored the variation in arousal, it has been suggested that this aspect of delirium phenomenology may be related to specific etiological factors (84,85). For example, a small study of patients with hepatic encephalopathy found that those patients were more likely to be hypoalert or somnolent than those in whom fever was the main etiological factor. In the latter group, patients were equally likely to have a somnolent (hypoalert) or a hyperactive (hyperalert) delirium (84). This study demonstrated a trend toward a hyperactive delirium in patients with alcohol withdrawal, an observation that is consistent with clinical experience. In another recent investigation, Meagher et al. reported that, in comparison with cases with an anticholinergic etiology, drugrelated cases of delirium had higher total scores on the Delirium Rating Scale and higher scores for perceptual changes, delusions, psychomotor disturbance, and mood lability (85). Drug-related cases also had higher scores than both the anticholinergic and infectious/electrolyte groups for changes in sleep-wake cycle and fluctuation of symptoms. More patients from the anticholinergic etiological group were likely to fit the hypoactive subtype. Except in cases of alcohol-related delirium, a definite relationship between etiology and clinical subtypes has not been consistently supported by neurodiagnostic studies (15,16). To date, no study has specifically described the phenomenology of delirium in cancer patients. Nonetheless, the diagnosis of delirium may be overlooked if the existence of differing phenomenologic subtypes, particularly the less apparent hypoactive delirium, is not recognized.

Specific attention disturbances are manifest not only by the level of arousal but also by changes in the patient's ability to concentrate, which can be subtle. Attention disturbances may be evidenced by an inability to maintain a conversation or to attend to its flow. Concentration may be assessed using a variety of assessment instruments for delirium (see the section Evaluation Instruments for the Assessment of Delirium). The Mini-Mental State Examination (86), for example, contains a specific question that seeks to define the patient's ability to concentrate by assessing the ability to subtract serial sevens or to spell the word “world” backward. Although specific assessment of concentration is an invaluable tool in the clinical evaluation of mental status, it is important to recognize apparent abnormalities of attention that may be influenced by language skills, hearing deficits, and other abilities or impairments (87,88).

The second *DSM* criterion for delirium relates to the presence of changed cognition—for example, disorientation; memory deficits; and disturbances of language, reasoning, and perception. It is important to recognize that a diagnosis of delirium may be established in the presence of any one of these cognitive abnormalities. For example, a patient who is not disoriented may still fulfill the criteria for a diagnosis of delirium if he or she is experiencing memory, language, or perceptual disturbances.

Orientation to time, place, and persons is one of the features most commonly associated with the syndrome. Although other features are also common, the perception that the prevalence of disorientation is high may, in part, be a consequence of the ease with which it is assessed. Clinical experience suggests that orientation in time is the first to be affected (10). Patients who are disoriented frequently locate themselves in a known space—for example, in a familiar hospital or house. Recognition of family and self is usually preserved, whereas the ability to recognize less well-known people, such as housestaff, is often lost. This hierarchical organization of person, space, and time orientation has also been observed in other conditions, such as the progressive recovery from electroshock (89).

Memory is another aspect of cognition that is often affected. Impairments in short-term memory are most probably due to the presence of attention failure. Remote memory can also be affected and more familiar memories appear to be retained more commonly than others—for example, patients frequently lose the ability to recall presidents' names before the name of their hometown (76). In addition to memory loss, memories may be disrupted and disorganized, with paramnesias and duplications (90).

Language abnormalities are frequently present in delirium and are often compounded by the presence of incoherent reasoning. Language may lack fluency and spontaneity, and conversation may be prolonged and interrupted by long pauses or repetitions. The language may reflect an inability to find the correct word or to name objects (anomia) and may be characterized by “passe-partout” words (nonspecific phrases that substitute for specific language, e.g., “you know what I mean”), stereotypes, and clichés. The general meaning of speech may be lost due to incoherence or the patient's inability to sustain attention. Chedru and Geschwind provided a series of unique observations on the neuropsychology of delirium and demonstrated that writing abilities are affected early and more severely than other language-related skills (91). More recently, in addition to dysgraphia, Baranowski et al. demonstrated that constructional apraxia was a useful clinical sign of delirium in the psychiatric inpatient population (92). This aspect of the neurological dysfunction can be useful in both the diagnosis and study of delirium. Assessment of these aspects of neurological function can be easily incorporated into bedside mental status examinations, but for this abnormality to be fully appreciated, it is optimal to have skilled interpretation of a substantial number of written words rather than simply a short written phrase.

Delirium may affect reasoning in complex ways. As the ability to reason and to think in the abstract requires intact attention, this aspect of cognition may be most difficult to evaluate. Nonetheless, patients frequently demonstrate irrelevant or rambling thinking, abnormal conceptualization, and altered insight with anosognosia (93).

Perceptual abnormalities may be more prevalent in particular delirium subtypes, such as DT. In some cases, these perceptions may be frightening and associated with agitated behavior. In one series of delirious medical and surgical patients, 24% experienced hallucinations, 18% delusions, and 9% illusions (84). Illusions and hallucinations usually involve visual phenomena, although auditory and tactile features may also be present. In another recent retrospective study of 227 delirious hospitalized patients evaluated by a psychiatry service, the prevalence of psychotic symptoms was 42.7%, with 27% of patients having visual hallucinations, 12.4% having auditory hallucinations, and 2.7% having tactile hallucinations (94). In this population, the presence of visual hallucinations, but not delusions or auditory hallucinations, was significantly associated with more active medical diagnoses and multiple etiologies causing the delirium.

Delusions may be associated with hallucinations. These delusions are frequently poorly organized and characterized by paranoid features, which may incorporate themes that relate, for example, to homicide, imprisonment, or jealousy. Occupational delusions are among the most common with the patient locating himself or herself in a familiar time and space and attending to usual activities. Lipowski describes “the law of the unfamiliar mistaken for the familiar” (10) and suggests that perceptions are influenced by the emotional color of the situation and the patient's personality characteristics. For example, doctors around the bed may be perceived to be ghosts announcing death. It has been observed that some patients may manifest similar delusional themes in more than one episode of delirium and in episodes

triggered by different etiological factors (10,95). In the study discussed above, Webster and Holroyd found that 25.6% of 227 delirious in-patients experienced delusions (94).

Although they are not among the diagnostic criteria, affective disturbances may characterize delirium. Such disturbances range from dysphoria to hypomania. The prevailing emotion of patients with delirium is probably anxiety (95). When insight is lost, mood often appears to be depressed and apathetic. The patient may suffer from his or her own confusion and may painfully try to keep focused and to understand the disease process and the surrounding world. There may be emotional lability, with fluctuating restlessness, irritability, anger, sadness, and anxiety. In the few available reports from patients recovering from delirium, the experience is usually described as a frightening, twilight dreamy state (10). Little is known about the associations that may exist between lack of insight, symptoms, and level of distress during episodes. A small study of 14 patients with cancer pain and severe cognitive failure found that during episodes of agitated cognitive failure, pain intensity as assessed by a nurse was significantly higher than the patient's assessment had been before and after the episode (4). On complete recovery, none of these patients recalled having had any discomfort during the episode. Although interpretation of these data is difficult, the authors suggest that patients who recover from a severe episode of delirium may have no memory of the experience, including the pain, and that medical and nursing staff are likely to overestimate the discomfort of patients with this condition. Another interpretation could be that patients with delirium are acutely sensitive to many irritating factors, including pain, noise, and other factors, and therefore risk becoming more distressed in the setting of delirium and such irritants [if, however, the latter interpretation were correct it would seem logical to consider careful titration of treatments directed toward both delirium *and* the irritant (e.g., pain) as a means of diminishing distress].

The third criterion for diagnosis of delirium relates to the time course of the disturbance. For diagnosis, there must be evidence confirming that the disturbance has developed over a short period of time and tends to fluctuate during the course of the day. This pattern of disturbance is characteristic of delirium, but as with the other diagnostic criteria, this pattern is not specific for delirium. The development of mental status changes over a short period may occur in other conditions, including certain types of dementia.

Fluctuation in the clinical manifestations of delirium is usually apparent in disturbance of the sleep-wake cycle. Patients usually experience insomnia and may be agitated at night and somnolent during the day. As noted previously, this change in sleep pattern is often found to be among the prodromal symptoms of the syndrome. The phenomenon known as “sundowning” refers to the worsening of symptoms toward evening and probably has more to do with sleep-wake abnormalities than with environmental factors (10).

In addition to mental status changes, described above, the neurological examination may identify findings associated with diffuse brain dysfunction, such as multifocal myoclonus and asterixis. Some findings may be relatively specific for one or more etiologies. For example, tremulousness is typical of alcohol withdrawal states; miosis and mydriasis suggest opioid toxicity and anticholinergic toxicity, respectively; and tachypnea may be a manifestation of a central process or of sepsis or hypoxemia.

The final *DSM* criterion for diagnosis requires evidence of a general medical condition judged to be etiologically related to the disturbance. The criteria do not state that proof of etiology is necessary. The implication of this criterion is that a medical condition that could feasibly have resulted in delirium must be present. As outlined in Table 39-2, numerous conditions can fulfill this criterion, including electrolyte disturbances, infection, fever, multisystem failure, and treatment with centrally acting drugs. A detailed history and physical examination may reveal findings that point to the etiology of the delirium and are therefore essential for establishing the diagnosis of delirium in addition to being essential for the assessment of treatment options (see the section Approach to Assessment).

In summary, a comprehensive history, combined with both careful observation and a mental status examination, will frequently provide evidence for the criteria necessary for a *DSM-IV* diagnosis (Table 39-1). A physical examination and review of laboratory data will frequently assist in defining the etiology of the syndrome.

CLINICAL FEATURES OF DELIRIUM IN SPECIFIC SUBPOPULATIONS

It is useful to distinguish several subpopulations in which the prevalence of delirium is high. Syndromes characterized by delirium may complicate withdrawal from alcohol and sedative-hypnotic drugs (96,97,98,99,100 and 101). Given that the lifetime prevalence of alcohol disorders in the United States is considered to be approximately 13% (102), alcohol is likely to be an important risk factor for delirium. In the oncology setting, the risk that alcohol withdrawal could be an etiological factor in delirium is increased in those populations who have tumors associated with alcohol consumption, such as those undergoing surgery for head and neck cancer (99).

The severity of alcohol withdrawal varies from minor symptoms of tremulousness through to the most severe form, DT (97,101). DT is usually seen in patients with a long history of alcoholism who are admitted to hospital for an intervening medical problem. Characteristically, these patients become delirious after 2 or 3 days, but symptoms may occur as late as 14 days after alcohol consumption has decreased or stopped (96,97,100). The onset is usually sudden, although the delirium may be preceded by tremulousness. It is characterized by agitation, tremors, vivid hallucinations, sleeplessness, and signs of autonomic hyperactivity. When hallucinations are related to withdrawal and DT, visual hallucinations tend to predominate, and auditory and tactile perceptual hallucinations are less common (103). Of note, alcoholic hallucinations may occur in the presence of a clear sensorium, as separate, isolated phenomena unrelated to delirium (98,101). These hallucinations are frequently auditory. Seizures may also occur in DT. In most cases, the withdrawal syndrome continues for <72 hours and is associated with spontaneous recovery, frequently followed by a period of deep sleep (101,104). DT can be associated with severe autonomic instability. This disturbance and intercurrent illness account for a mortality for DT between 5% and 15%.

Delirium is common in the postoperative setting. Numerous factors may contribute to a higher likelihood of delirium in this setting, including pain medications, anaesthetic agents, medical illness, and other factors (39). Although this group of patients has been extensively investigated, there have been no studies to suggest that the clinical picture in postoperative delirium is significantly different than delirium from metabolic disturbances or other causes. Those who experience delirium in the postoperative setting have a higher mortality, lesser functional recovery, and longer hospital stays than those who do not develop this complication (6,33,53,105).

Delirium is highly prevalent in patients with advanced terminal illness who are approaching the end of life (37,38,42,43,45,54,58). Accordingly, the assessment and treatment of mental status changes are a very important aspect of palliative care. “Terminal restlessness” is a term that is frequently used to describe the clinical appearance of some patients as they approach death. This condition could, most often, be more accurately described as “agitated delirium in a dying patient” (106). Unfortunately, this particular subgroup of patients has rarely been studied using strict diagnostic criteria for delirium. Although surveys of the last few weeks of life frequently cite “confusion” as a problem, this term does not provide diagnostic specificity. Clinical experience and some recently studies suggest that terminal delirium is prevalent in the hospice and palliative care setting (37,38,42,43,45,54,58) and may be associated with multifocal myoclonus and convulsions. The etiology of the delirium is likely to be multifactorial, with metabolic and drug-related factors in the setting of multisystem failure being contributory. Lawlor et al. found that psychoactive medications, predominantly opioids, dehydration, hypoxic encephalopathy, metabolic factors, and nonrespiratory infection were common associations with delirium in this setting (43).

APPROACH TO ASSESSMENT

Assessment of the patient with a change in mental status should seek to both clarify the diagnosis and define the etiology of the change. Assessment should also aim to provide the clinician with a view of the patient in the context of the overall medical condition. This view should include an understanding of both the impact of the symptoms and disease and the goals of treatment. The latter is imperative, as the patient's and family's goals of care, particularly in case of advanced illness, will influence decisions regarding the extent of the diagnostic workup and the options for interventions.

A thorough evaluation should be considered when any change in mental status is observed (see the section Mental Status Changes and Clinical Applications of Diagnostic Criteria). This applies not only to the presence of “confusion” and prominent psychiatric symptoms, such as hallucinations and paranoia, but also to other psychological symptoms, including anxiety, fear, sleep disturbance, somnolence, and others (Table 39-3). Each of these symptoms may be components of delirium. In assessment, it is important to consider symptoms as multidimensional experiences that may be evaluated in terms of their specific characteristics and their impact (79,107,108,109 and 110). The symptoms associated with delirium should be assessed in terms of their frequency, severity, and distress. Psychiatric symptoms must be assessed also in relation to their perceptual characteristics and the patient's interpretation of their meaning (111). The impact of symptoms and the mental status changes associated with the overall syndrome should be explored in relation to the patient's level of distress; family or caregiver distress; behavior patterns, including behavior that may predispose to injury; and spheres of functioning.

A full medical history is a vital component of the workup of delirium. The degree to which the patient can respond cogently is an important part of the evaluation (111). Even when the patient is capable of giving the history, insight may be lacking as a direct consequence of the evolution of the delirium. An interview with those caring for the patient, perhaps family or nursing staff, may be necessary. For example, nighttime symptoms or subtle evidence of cognitive impairment may have been noticed by the caregivers and not by the patient. The interview must also explore the patient's medical and psychiatric history, systems review, social and family history, medications, previous drug reactions, and allergies. Some symptoms, such as fever, may assist in establishing the etiological factors. All drugs consumed by the patient in the days preceding the episode should be carefully reviewed, with attention to the pattern of administration and dosing in relation to the delirium. Although the extent of the disease may in some cases be known, in others this may need to be defined.

As discussed above in relation to the *DSM* criteria, physical examination, including a mental status and neurological examination, should seek to define the

neurological and psychiatric syndrome (112,113) and should assess for evidence of potential contributory factors, including sepsis, dehydration, or major organ failure. Given the importance of the detection of subtle changes in mental status for detection and diagnosis of delirium, assessment of baseline mental status should be routine in the assessment of patients with acute illness or before the administration of therapies that may precipitate delirium. The use of an evaluation instrument may be useful for both baseline and ongoing assessment (see the section Evaluation Instruments for the Assessment of Delirium).

Assessment of laboratory parameters will allow assessment of the possible role of metabolic abnormalities, such as hypercalcemia, and other problems such as hypoxia or disseminated intravascular coagulation (Table 39-5). Bedside assessments, such as oxygen saturation and blood glucose, may also provide important information. The choice of investigations should be guided by the clinical situation and the goals of care. EEG may supplement the clinical assessment and assist in the clarifying the diagnosis, particularly if there is concern that the differential diagnosis includes epileptiform activity or central nervous system pathology characterized by specific EEG findings. Similarly, brain imaging studies and assessment of the cerebrospinal fluid may be useful when considering the evaluation of etiological factors.

Blood glucose
Electrolytes (sodium, potassium, chlorine, calcium)
Urea and creatinine
Oxygen partial pressure, carbon dioxide partial pressure, bicarbonate, pH (arterial blood)
Full blood count
Osmolality
Other blood tests may be indicated, including, among others, VDRL; heavy metal screen; tests for vitamin B_{12} and folate levels; tests for lupus erythematosus, antinuclear antibody, urinary porphyrins, ammonia, human immunodeficiency virus, antineuronal antibodies
Electrocardiogram
Cerebrospinal fluid examination: Blood, glucose, protein, cells, culture
Screen for disseminated intravascular coagulation
Liver function tests
Infection screens: Blood, urine, and other cultures
Thyroid and adrenal function tests
Head computed tomography scan or magnetic resonance imaging
Electroencephalography

TABLE 39-5. DIAGNOSTIC TESTS TO CONSIDER IN A PATIENT WITH DELIRIUM

Studies in patients with advanced cancer have demonstrated the usefulness of this thorough diagnostic assessment (38,64,65,114). One study found that 67% of delirious cancer patients improved with treatment (64). This improvement was achievable even in a population in whom delirium was a poor prognostic factor for overall outcome—the 30-day mortality was 25%, and 44% of patients died within 6 months (usually from progression of the underlying cancer). Another study found that one-third of the episodes of cognitive failure improved after an evaluation that yielded a cause for these episodes in 43% (38). Lawlor et al. also found that reversal of delirium occurred in 49% of 94 episodes in 71 patients with far advanced cancer (43). Each of these studies confirms the usefulness and importance of a vigilant and active approach to the diagnosis and treatment of delirium—even in the setting of far advanced disease.

DIFFERENTIAL DIAGNOSES OF DELIRIUM

Although the most important diagnoses to be differentiated from delirium are dementia and other psychiatric conditions, the differential diagnosis of delirium encompasses almost the whole spectrum of psychiatric disease as well as an array of neurological disorders (12,115). As discussed previously, it is most important for clinicians to be cognizant of the spectrum of symptoms that may be features of delirium and aware that almost any psychiatric symptom may be a manifestation of delirium. As a consequence, the mental status examination is an important aspect of the assessment of all psychiatric symptoms in the cancer patient, including anxiety, tearfulness, nervousness, depression, irritability, and others. Although these symptoms may be within the normal spectrum of response to serious illness or represent a primary psychiatric disorder, they could indicate a subtle delirium.

When the mental status examination reveals impaired cognition, the potential diagnoses include delirium, dementia of various types, amnestic disorders, and druginduced disorders. The *DSM-IV* categorizes this group as “cognitive impairment disorders” (7). Table 39-4 reports some of the features that facilitate the differentiation of these conditions (82).

The dementias are characterized by progressive cognitive impairment. A history of a chronic decline without alteration in level of arousal assists in distinguishing these syndromes from delirium. Nonetheless, the assessment can be challenging. Dementia increases the risk of delirium and the two conditions may occur concurrently, particularly in the elderly. Demented patients are particularly sensitive to drug toxicities, especially to drugs with anticholinergic activity, and to metabolic and physical stress, including surgery (51). A history of the patient's baseline mental status, level of cognitive impairment, and behavioral pattern is important in the assessment of the demented patient who may be experiencing delirium.

The acute psychoses also can be difficult to differentiate from delirium. The term *pseudodeliria* has been introduced to describe these episodes, which usually occur in patients with a psychiatric history (82). Vigilance is usually preserved and the EEG is normal. Delusions tend to be more systematized and bizarre in cases of psychosis. A patient with a known history of psychiatric disease who develops an episode of confusion requires careful screening of possible organic causes.

Mood disorders are also common, both in the elderly and in the cancer population, and may contribute to diagnostic uncertainty in the evaluation of cognitive impairment (35,36,44,48,116,117,118,119 and 120). Although mood disorders, in particular depression, are common, depressive symptoms are also a common manifestation of delirium. A study of elderly patients found that 42% of the patients who were referred for evaluation of depressive symptoms had a diagnosis of delirium (48). This diagnosis had been considered by the referring health care provider in only 3% of cases. The high prevalence of both mood disorders and delirium in the ill population serves to emphasize the need for a comprehensive assessment that incorporates neurological, psychiatric, and cognitive evaluation.

It is well known that cognitive functions may be affected by brain lesions. When metastases or other structural disease is possible, a full assessment of cognitive impairment must include a comprehensive neurological examination, including aspects of speech and other higher cortical functions (12). An apparent case of delirium manifest by language disturbance may be found, on further examination, to relate to a dysphasic syndrome secondary to a focal cerebral lesion.

Finally, the diagnosis of delirium can be challenging when isolated aspects of the disorder occur without fulfilling the criteria for delirium. Just as depressive symptoms may occur in a patient who does not meet the criteria for a formal psychiatric diagnosis (119,120 and 121), drug-induced hallucinations may occur in isolation without cognitive impairment (122). As alluded to above, the presence of isolated symptoms should prompt comprehensive assessment, monitoring, and, if necessary, treatment to minimize distress.

EVALUATION INSTRUMENTS FOR THE ASSESSMENT OF DELIRIUM

Instruments useful in delirium assessment include those developed for the assessment of cognitive impairment and those specifically developed for the assessment of delirium (Table 39-6) (123,124 and 125). These instruments can be used to identify and quantify cognitive impairment and to determine the likelihood that the impairment can be ascribed to the diagnosis of delirium. As the *DSM-IV* criteria define cognitive impairment as a component of delirium, the abnormalities found on screening tests for cognitive impairment, although not diagnostic of delirium, can be useful in alerting the clinician to the presence of cognitive impairment. Smith et al. comprehensively reviewed the evaluation tools for delirium assessment (124).

Diagnostic classification systems
DSM-III (132), *DSM-III-R* (9), *DSM-IV* (7), *ICD-9* (211), *ICD-10* (212)
Instruments for assessment and screening for cognitive impairment
Mini-Mental State Examination (86)
Short Portable Mental Status Questionnaire (213)
Cognitive Capacity Screening Examination (214)
Blessed Orientation Memory Concentration Test (126)
Other screening instruments, checklists, and algorithm methods
Confusion Rating Scale (215)
Saskatoon Delirium Checklist (216)
Confusion assessment method (128)
Diagnostic interviews
Delirium symptom interview (129)
Delirium rating scales
Delirium Rating Scale (DRS and DRS-R-98) (130,131)
The Memorial Delirium Assessment Scale (133)
Laboratory examinations
Electroencephalogram, brain imaging
Serum anticholinergic activity

TABLE 39-6. EVALUATION METHODS AND INSTRUMENTS FOR DELIRIUM ASSESSMENT AND RESEARCH IN CANCER PATIENTS

Instruments for assessment of cognitive impairment include the Mini-Mental State Examination (86) and the Blessed Orientation-Memory-Concentration Test (126). Although these tools are sensitive indicators of cognitive impairment (37,38,127), the diagnosis of delirium requires further assessment with either a clinical interview or the administration of another validated instrument.

The clinical psychiatric interview using the *DSM* criteria remains the gold standard for the evaluation and diagnosis of delirium (7,111). Instruments that are available to facilitate the diagnosis (124) include the confusion assessment method (128), the delirium symptom interview (129), and the Delirium Rating Scale (130,131). These instruments were initially developed based on the earlier criteria outlined in the *DSM-III* (132) or *DSM-III-R* (9) and use an interview format to characterize the features of the cognitive impairment. Many of these instruments use either a score above a cutoff point or an algorithm to document the presence or absence of delirium but do not address severity. With the exception of the one instrument discussed below, none of the currently available instruments has been adequately validated as a measure of delirium severity. Trzepacz et al. further validated the Delirium Rating Scale (Delirium Rating Scale-revised-98) (131). This 16-item clinicianrated scale has 13 severity items and three diagnostic items, and this recent validation study found it to be a valid measure of delirium severity over a broad range of symptoms, thus suggesting that it may have diagnostic and assessment use and be useful in longitudinal studies. The Memorial Delirium Assessment Scale is a rating scale that has undergone early validation studies in patients with cancer and human immunodeficiency virus and may prove a useful clinical and research tool, especially in these populations, if further studies confirm its usefulness (133). Instruments may have a useful role in providing a method for the monitoring of patients predisposed to delirium or receiving treatment for this condition. Although this potential exists, many of the instruments used to date in screening have lacked adequate validation for this purpose (123,124). With the availability of the recent validation information about the Delirium Rating Scale-revised-98, this instrument may prove to be useful in this regard (131).

The instruments for delirium diagnosis have an important role in research, but none has been widely used in routine clinical practice. Their use in this manner could focus staff attention on assessment and be used to review the quality of patient care and situation-specific barriers to symptom control (37,134,135 and 136). In considering routine use, simplicity and brevity are important features. For this reason, some clinicians have selected the Mini-Mental State Examination (86) for routine monitoring (37,134,135,136 and 137). If using the instrument for this purpose, clinicians should be aware that it has population-specific limits relating to age, language, and education (87,138). In addition, as mentioned previously, the instrument does not fully assess the criteria necessary for a diagnosis of delirium.

TREATMENT

The management of delirium comprises interventions directed at symptom control and interventions directed at underlying causes (64,114,115,127,139,140 and 141). The degree to which these treatments are pursued is determined by the goals of care. It is important, especially when discussing treatment, to consider issues of competency and consent. Patients with delirium are frequently medically ill, and, oftentimes, complex treatment decisions must be made during or around an episode of delirium. Such decisions may involve the treatment of the underlying disease, the establishment (or reestablishment) of goals of care, and specific treatments for delirium. Unfortunately, the nature of delirium itself and its impact on concentration, insight, and cognition in general may interfere with the ability of a patient to make such decisions. Although delirium does not always equate with lack of capacity to give informed consent, this issue must be considered, monitored over time, and formally assessed when decisions are to be made. Respect for the patient's previously defined wishes must be considered in settings in which the patient is not competent, and involvement of the health care proxy is crucial in these settings (139).

Etiological Interventions

As discussed previously, the etiology may be related to one factor or many factors (Table 39-2). Although in advanced disease the goals of care may dictate a limited workup, the identification and correction of the underlying cause(s) should be pursued, to whatever degree is appropriate and feasible, concurrently with the implementation of symptomatic therapies. In complex cases, it may be possible to address at least one, if not several, of the etiological factors. For example, a drug-induced delirium may be ameliorated by dose reduction, if feasible, or by switching to an alternative drug. Even those patients in whom the etiology of delirium is multifactorial may be observed to benefit after reversal of one or more factors (37,43,64,75,142,143). In addition, certain problems can be difficult to diagnose but suspected clinically, and such problems may warrant empirical treatment. For example, in patients with delirium who have a reason to be deficient in vitamin B (e.g., those who have problems with alcoholism or malnutrition) multivitamin replacement should generally be given (139).

In many patients, drugs are contributory factors in delirium (43,64). All nonessential drugs should be stopped (or tapered if that is the appropriate method of cessation for the particular medication). When opioid-induced delirium is the most likely diagnosis, it may be useful to institute a switch from one opioid to another (144,145 and 146). Although no opioid has been shown to have a more favorable central nervous system side effect profile than any other, this practice may identify a drug with a more favorable balance between analgesia and side effects in an individual patient. Bruera et al. suggested that in terminal cancer patients careful monitoring of cognitive function, attention to dehydration, and opioid rotation can reduce the incidence of agitated delirium and the need for neuroleptic medication (145).

Behavioral and Environmental Management

Treatment measures for delirium, regardless of cause, include the manipulation of the environment to provide a safe, quiet, and reorienting milieu and support and reassurance through communication with the patient and family. Where possible, measures should be implemented that increase structure and familiarity and reduce anxiety and disorientation. These measures may include encouraging the family to sit with the patient and placing the patient in a quiet, well-lit room with familiar personnel. The use of orienting devices, such as clocks, calendars, and familiar objects from the patient's home, may be useful. In a randomized prospective trial, discussed above, Inouye et al. used both behavioral and environmental interventions aimed at reducing delirium risk factors and with these effectively reduced the incidence of delirium in hospitalized elderly patients (57). In this population, the significant findings were that delirium developed in 9.9% of the intervention group, as compared with 15% of the usual-care group, and the total number of days with delirium and the total number of episodes were significantly lower in the intervention group. However, the severity of delirium and recurrence rates were not significantly different (57).

The safety of the patient with delirium must be ensured. One-to-one nursing observation may be necessary. Occasionally, physical restraint may be needed for a brief time to prevent harm to the patient and others. The use of physical restraints must be minimized, implemented strictly according to national and institutional policies and regulations, and relinquished as soon as behavioral control is attained with drugs.

Patient and family counseling is an important part of delirium treatment. At any time, but especially when the condition is associated with terminal disease, the communication difficulties associated with the condition may cause distress in family members (147). Table 39-7 highlights some of the issues that should be addressed in family counseling. Although psychological expertise may be helpful in complex cases, a discussion between the physician and family will usually suffice to allay family concerns, guide the family's approach to the patient, and assist them in decision making. Importantly, a family member is frequently the proxy for health care decision making for the cognitively impaired patient, and for this reason as well as many others, family members should be kept apprised of the patient's medical condition.

Communication barrier
Patient's awareness of physical and psychological suffering
Reversibility
Short-term prognosis
Fluctuations of cognitive functions
Role of opioid and other therapies in etiology
Role and goal of sedation
Goals of care

TABLE 39-7. CRITICAL ISSUES IN COUNSELING FOR THE FAMILY OF DELIRIOUS PATIENTS

During an episode of delirium, the patient may experience fear related to an awareness of the impairment. In such circumstances, the patient may require repeated reassurance. The importance of patient counseling before the potential onset of postoperative delirium and of systematic reorientation during the episode has been demonstrated in two studies (148,149). These studies confirm the often cited importance of environmental approaches directed to maximizing safety and providing psychosocial support (150,151).

Pharmacological Therapy

Symptomatic treatment of delirium is often, but not always, necessary. It is appropriate, while treatment is being instituted for etiological factors, to alleviate distress in severe cases, to reduce the risk of mortality in DT, and to manage cases with unknown or untreatable etiologies. Except in the case of DT, for which a benzodiazepine is the first-line drug, a neuroleptic is generally the most appropriate drug for the initial management of delirium (Table 39-8). Although for some time this has been the accepted approach, a recent study of symptoms of delirium in medically hospitalized acquired immunodeficiency syndrome patients provided evidence of the efficacy of this approach (152). Breitbart et al. demonstrated that delirium can be treated efficaciously and with few side effects by using lowdose neuroleptics (haloperidol or chlorpromazine) and that the use of benzodiazepines alone, specifically in this case lorazepam, appeared to be ineffective and associated with treatment-limiting adverse effects (152). Of note, the benefits of treating mild delirium without distress have not been established. In addition, the value of neuroleptic therapy has not been confirmed in hypoactive delirium although psychostimulants have been suggested for the treatment of the this condition (135,153,154).

Drug	Commonly used routes
Neuroleptics	
Haloperidol	Oral, intramuscular, intravenous, subcutaneous
Droperidol	Intravenous, intramuscular
Thioridazine	Oral
Chlorpromazine	Oral, intramuscular, intravenous
Methotrimeprazine	Oral, subcutaneous
Benzodiazepines	
Lorazepam	Oral, intramuscular, intravenous
Midazolam	Intravenous, subcutaneous

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TABLE 39-8. COMMON MEDICATIONS USED FOR THE MANAGEMENT OF DELIRIUM IN ADULT CANCER PATIENTS

To date, haloperidol has generally been considered the drug of choice for hallucinations and agitation related to delirium in the medically ill (10,37,134,139,151,152,155,156,157,158,159,160,161,162,163 and 164). Comparative trials are lacking in this area but the clinical preference tends to be for haloperidol, with this preference based on both clinical experience and anecdotal evidence (10,127,139,162). Haloperidol is a potent dopamine blocker with useful sedating effects and a relatively low incidence of cardiovascular and anticholinergic effects. Other neuroleptic drugs may also be efficacious— for example, thioridazine, droperidol, and chlorpromazine. The recent American Psychiatric Association's Practice guidelines cite droperidol, a butyrophenone with a rapid onset of action and relatively short half-life, as having some use for agitation in the hospital setting; these guidelines suggest that this medication, which is more sedating than haloperidol, may have its main use in hospitalized patients with agitation, as there is some evidence to suggest a more rapid response may be obtained with droperidol than with haloperidol (165,166). The role of the newer antipsychotic drugs with fewer extrapyramidal side effects and with activity on dopamine, serotonin, and histamine receptors (e.g., risperidone, olanzapine, and clozapine) has not to date been clarified (167,168,169,170,171 and 172). A few case reports have been published reporting the use of these atypical neuroleptics (139,172,173,174 and 175). To date, these medications have not been widely used for delirium, but it will be important for their role to be explored in future studies.

Haloperidol has been used via the oral, intramuscular, intravenous, or subcutaneous route. The oral route may be appropriate in mild delirium cases; agitation and uncooperative behavior necessitate parenteral administration. Although the intravenous route has not been approved by the U.S. Food and Drug Administration, this route has been reported to be safe and effective (176,177 and 178) and is widely used for treatment of delirium in the severely ill (139,162,177). The subcutaneous route has been frequently used in the palliative care setting (66,127,179). Parenteral doses of haloperidol are roughly twice as potent as oral doses, and clinical effects are usually observed within 30 minutes after intravenous administration and may last for 4–8 hours (162). The half-life of haloperidol is between 14 and 20 hours and the drug is widely distributed and may remain in the body for long periods (180,181).

Empirical guidelines have been proposed for the treatment of delirium (139,162,164,177). There have been few studies to determine the optimal doses of antipsychotic medications in the treatment of delirium. On the basis of doses used in several studies, for very agitated delirium, starting haloperidol in the range of 1–2 mg parenterally every 2–4 hours as needed has been suggested with appropriate monitoring (see below), and low doses, for example, as low as 0.25–0.50 mg of haloperidol every 4 hours as needed, have been suggested for elderly patients (139). Some guidelines mention the use of either droperidol or haloperidol for very agitated cases. The dose can be repeated after 20–30 minutes—and if this is needed it is usually recommended only with a limit of 5 mg of haloperidol every 15 minutes, again with appropriate monitoring (see below). Generally, unless agitation is very severe, dosing should be titrated against symptoms at intervals of 45–60 minutes (182). Typical doses are likely to range between 0.5 and 20 mg of haloperidol administered in the first hour. When the patient is calm, haloperidol is continued by either the oral or parenteral route. The usual dose is 0.5–3.0 mg of haloperidol one to three times daily, which can be given on an as-needed basis or on a fixed schedule. When delirium is mild, treatment can be initiated with haloperidol, 1–2 mg orally or 0.5–1.0 mg parenterally.

Although most guidelines recommend initial treatment with small doses (139), published series have actually reported varying dose regimens. For example, one study of less severe cases, which included hypoactive delirium, noted that low doses (3 mg) of haloperidol appeared to improve symptoms (183). A survey of the management strategies used for intoxicated or head trauma patients observed that average cumulative doses of 8.2 mg were helpful in reducing aggressive behavior (156). A study of acquired immunodeficiency syndrome delirium reported symptomatic improvement with combination therapy of haloperidol (average daily dose of 42 mg) and lorazepam (average daily dose of 7.5 mg) (158), and surveys in intensive care units have reported the use of high doses of intermittently administered or continuously infused haloperidol (48–1155 mg/day) (182,184,185). Despite the high doses administered in the latter studies, clinical experience would suggest that most patients respond to doses of <20 mg of haloperidol in a 24-hour period.

A drawback to the use of haloperidol and other neuroleptic drugs is the potential for extrapyramidal side effects and movement disorders (37,186). Acute dystonias and other extrapyramidal side effects generally respond to antiparkinsonian medications, including diphenhydramine, benztropine, and trihexyphenidyl. Akathisia may respond to low doses of either propranolol (5 mg two to three times per day) or lorazepam (0.5–1.0 mg two to three times per day) (187). A trial of benztropine (1–2 mg once or twice per day) may prove to be useful; however, this medication is not generally used as a first-line treatment for akathisia (187). It is important to be vigilant for this latter side effect, which may go unnoticed in a patient with restlessness associated with the delirium itself.

A rare and serious complication of neuroleptic medications is the neuroleptic malignant syndrome, which may occur as an isolated event or may be triggered by a concurrent illness or fever (186,188). This syndrome may be fatal and must be treated as a potential medical emergency. Although neuroleptic malignant syndrome usually occurs after prolonged, high-dose administration of neuroleptics, it may occur spontaneously in patients on lower doses. It is characterized by hyperthermia, increased confusion, leukocytosis, muscular rigidity, myoglobinuria, and high serum creatine phosphokinase. Treatment measures should include discontinuation of the neuroleptic, general supportive measures, treatment of precipitating factors, and the use of dantrolene sodium and bromocriptine mesylate (186,188).

In addition to its neurological side effects, haloperidol may be associated with cardiac arrhythmias (e.g., torsade de pointes, ventricular fibrillation, and sudden death) through prolongation of the QT interval on the electrocardiogram (189,190,191 and 192). The American Psychiatric Association has made specific recommendations in its practice guidelines, as have others about this problem (139,189,190,191 and 192). In summary, the guidelines recommend that medication management include a baseline electrocardiogram, with special attention paid to the length of the QTc interval. If the baseline QTc interval is ³440 msec, or >25% over that in previous electrocardiograms, the patient may warrant telemetry, a cardiology consultation, dose reduction, or discontinuation of the antipsychotics. The same approach is recommended for patients receiving other drugs that may prolong the QTc interval or those that have electrolyte disturbances. It has also been recommended that serum levels of magnesium and potassium be monitored, and attention should also be given to widening of the QT interval that may occur during administration of these medications in critically ill patients. Special attention should be given to those receiving doses of >50 mg/24 hours, as these patients appear to be at greatest risk for development of conduction disturbances. It is important to note that goals of care may also influence the degree to which monitoring is appropriate. It may, for example, be acceptable to treat a dying patient who has clearly defined goals of care that are focused on comfort alone with less intense electrocardiographic and electrolyte monitoring. The common occurrence of delirium at the end of life speaks to the need and importance of establishing and maintaining clarity with respect to goals of care with the patient or their health care proxy throughout the course of advanced illness.

Haloperidol alone may fail to control the symptoms of delirium. In such cases, either a benzodiazepine or another sedative, or a neuroleptic other than haloperidol, can be added. Anecdotal experience is greatest with lorazepam and midazolam. Clinical experience, along with one case series in the cancer population, confirms the need for the use of more than one drug for delirium management in patients with advanced cancer (37). Of the 39 cancer patients reported in the one reported series, 20% were controlled with haloperidol alone, 13% with lorazepam alone, 26% with a combination of lorazepam and haloperidol, and 40% needed another neuroleptic medication (chlorpromazine or methotrimeprazine). Overall, 26% of the patients needed sedation, usually achieved with midazolam, to control delirium.

The choice of a second drug in the management of delirium should be guided by the drug pharmacokinetics and side effects profile and by the goals of care. For example, propofol, midazolam, or lorazepam has been recommended in the critical care setting because the pharmacokinetics of these drugs favor rapid dose titration in the initial phases of treatment (162). Chlorpromazine is not recommended in these circumstances because of the likelihood of hypotension and other anticholinergic effects. When sedation would be an acceptable or even favorable outcome, for example, in the terminal setting where the patient has lost the ability to interact, chlorpromazine or a benzodiazepine may be a valuable drug. Other factors may also be considered in some patients: The patient with hypotension should be treated with the medication with the least effect on blood pressure, and the delirious postoperative patient who has an ileus or urinary retention should receive the antipsychotic medication with the fewest anticholinergic effects.

In contrast to neuroleptic drugs such as haloperidol, benzodiazepines do not serve to clear a delirious patient's sensorium or improve cognition. As discussed above, in a double-blind randomized trial comparing haloperidol, chlorpromazine, and lorazepam, Breitbart et al. demonstrated that lorazepam alone, in doses up to 8 mg in a 12-hour period, was ineffective in the treatment of delirium and contributed to worsening cognitive impairment (152). Both of the neuroleptic drugs, in low doses (approximately 2 mg of haloperidol equivalent/24 hours), were highly effective in controlling the symptoms of delirium and in improving cognitive function. Benzodiazepines should not, therefore, be considered as first-line treatments for delirium but rather as sedatives that may be useful to reduce agitation. In some cases, particularly in the last days of life, clearing the sensorium and improving cognition may not always be attainable goals. The processes causing delirium may, as death nears, be ongoing and irreversible. Ventafridda, Fainsinger, and their respective colleagues have reported that a group (10–50%) of terminally ill patients experience delirium that can be controlled only by sedation to the point of a significantly decreased level of consciousness (134,136,193). In such cases, and occasionally in the course of management of reversible delirium, a common strategy in the management of agitated delirium is to supplement the regimen of haloperidol with parenteral benzodiazepine (158,182).

Lorazepam is generally considered to be the drug of first choice when a benzodiazepine is necessary. This drug undergoes glucuronidation and has an intermediate half-life. These characteristics and the observation that lorazepam, unlike other benzodiazepines, has no active metabolites have suggested the superiority of this drug when treating elderly patients or patients with liver disease (194). It can be safely administered even in the critically ill (162,195,196 and 197). Dosing usually begins at doses of 1–2 mg orally in mild cases or 0.5–2.0 mg (0.044 mg/kg) administered intravenously or intramuscularly in severe cases (162,197). This medication can be administered by the oral, intramuscular, or intravenous route.

Some authors have expressed a preference for the use of midazolam for the management of delirium. It has been reported to be of use in cases of agitated delirium attributed to the excitatory effects of high-dose opioids and for the management of terminal delirium (106,198). Although theoretically any benzodiazepine may be useful for the latter indication, midazolam can be administered via the subcutaneous route, which can be viewed as a significant advantage in the palliative care setting (106,198).

During acute dosing, midazolam is short-acting and has a rapid onset of effect (within minutes) (162). Reported dose ranges have been between 20 and 60 mg/day although higher doses (up to 200 mg/day) have been administered without untoward incidents (106,198). The drug is rapidly redistributed and is likely to require continuous infusion to maintain its effects. Long-term administration results in prolongation of the clinical effects of the drug. Active metabolites can accumulate in liver failure. These factors contribute to the observation that midazolam is associated with a less rapid awakening than lorazepam. Consequently, midazolam is considered to be less suitable for use when prolonged treatment is likely to be needed and recovery is expected (162). Aside from its pharmacokinetic profile, the comparative cost of this drug has also been cited as a reason for a preference for lorazepam when prolonged treatment is required (162).

Methotrimeprazine is also commonly used to control confusion and agitation in the setting of terminal disease (199). Dosages range from 12.5 mg to 50.0 mg every 4–8 hours, up to 300 mg/24 hours. Hypotension and sedation may limit the use of this drug. However, often the goal of treatment with this medication, as with midazolam, may be to achieve quiet sedation at the end of life.

Alcohol withdrawal and sedative hypnotic withdrawal are special cases of delirium in that their treatment relies on the use of benzodiazepines (97,99,100,103,194,200,201,202,203 and 204). In alcohol withdrawal, benzodiazepines are recommended both to prevent the severe manifestations of DT in patients with minor symptoms of withdrawal and for first-line treatment. This “prophylactic” role in high-risk patients with mild withdrawal has not been explored for delirium related to other etiological factors and currently is unique to the management of the alcohol withdrawal syndrome. The risk of seizures and the high mortality of this condition are factors that contribute to need for early treatment. Diazepam, chlordiazepoxide, and lorazepam are the most commonly used benzodiazepines but, to date, controlled trials have not settled the ongoing debate as to which of these medications is the drug of first choice (194). Haloperidol may be useful, however, in the management of alcohol-related hallucinations.

PROGNOSTIC ISSUES

The resolution of delirium is likely to depend on many factors and the course may be complicated. Although frequently the clinical perception is that the condition is transient and brief, in a study of elderly delirious patients, the average duration of an episode was found to be >2 weeks (19.5 ± 15.4 days) (6). In this group, the most common etiologies for delirium were stroke, infections, and metabolic disorders; coexistent structural brain disease was present in many (81%). Levkoff et al. evaluated a group of acutely hospitalized elderly patients and demonstrated that among those with delirium resolution of symptoms was often incomplete, with only 4% experiencing resolution of all new symptoms before hospital discharge, and 20.8% and 17.7% had symptom resolution by 3 and 6 months, respectively (33). To complicate this issue further, many patients experience delirium in the terminal phases of illness, and although it is common that this condition is reversible—even in advanced illness—in the immediate days before death, many patients have no resolution of symptoms (38,43,45,54). In the Levkoff et al. study, almost one-third of the group members were found to be experiencing individual symptoms of delirium, although they did not meet the full criteria. These data suggest that delirium may be substantially less transient than currently believed and that incomplete manifestations of the syndrome may be frequent.

The mortality associated with delirium has been reported to be between 10% and 65% (6,33,34,205,206). Delirium is more frequent in patients with multiple medical problems, and it is likely that these processes, rather than the delirium itself, contribute to the high mortality rate. Nonetheless, delirium has been shown to be an indicator of poor prognosis (2,58,207). In the elderly, the presence of delirium identified those patients at risk for prolonged hospitalization, loss of independent community living, and future cognitive decline (208,209 and 210). In a population of advanced cancer patients, Caraceni et al. found that the survival curve of patients with delirium was significantly different from that of nondelirious patients, with delirium having a negative impact on prognosis (58).

CONCLUSION

Delirium is a highly prevalent disorder in medically ill cancer patients and is associated with both patient and family distress. Frequently, this condition presents significant management problems. In many instances, delirium is overlooked in the clinical setting, and a vigilant and thorough approach to detection and assessment is essential. Given that delirium is frequently reversible, the management should align with the overall goals of care for the patient and appropriate treatment strategies should be implemented based on detailed assessment of contributory factors. Further research is needed to assess many aspects of this condition, both in the general medical population and the oncology setting.

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40

DEPRESSION AND ANXIETY

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Emotional distress is a normal response to a catastrophic event such as the diagnosis of cancer or another life-threatening medical disease. The diagnosis of cancer induces stresses that are caused by the patient's perceptions of the disease, its manifestations, and the stigma commonly attached to this disease. For most individuals, the primary fear is a painful death. Patients also fear becoming disabled and dependent, having altered appearance and changed body function, and losing the company of those close to them. Each of these fears is accompanied by a level of psychological distress that varies from patient to patient. This variability is related to medical factors (e.g., site and stage of illness at the time of diagnosis, treatments offered, course of the cancer, and the presence of pain); psychological factors (e.g., prior adjustment, coping ability, emotional maturity, the disruption of life goals, and the ability to modify plans); and social factors (e.g., availability of financial and emotional support from family, friends, and coworkers) (1). Understanding these factors allows the clinician to predict and manage distress that exceeds a threshold arbitrarily defined as normal. The presence of intolerable distress or prolonged distress that compromises the usual function of the patient requires evaluation, diagnosis, and management.

NORMAL RESPONSES TO THE STRESS OF CANCER

Individuals who receive a diagnosis of cancer, or who learn that relapse has occurred or treatment has failed, show a characteristic emotional response: a period of initial shock and disbelief, followed by a period of turmoil with mixed symptoms of anxiety and depression, irritability, and disruption of appetite and sleep. The ability to concentrate and carry out usual daily activities is impaired, and thoughts about the diagnosis and fears about the future may intrude (2). These normal responses to crisis or transitional points in cancer resemble the response to stress that has been described in relation to other threatened or actual losses (3,4,5 and 6).

These symptoms usually resolve by 7–10 days with support from family, friends, and a physician who outlines a treatment plan that offers hope. Interventions beyond those provided by physicians, nurses, social workers, and clergy are generally not required, unless symptoms of emotional distress interfere with function or are prolonged or intolerable. Prescribing a hypnotic (e.g., zolpidem tartrate or triazolam) to permit normal sleep and a daytime sedative (e.g., a benzodiazepine, such as alprazolam or lorazepam) to reduce anxiety can help the patient through this crisis period. Some patients continue to have high levels of depression and anxiety (both are usually present, although one may predominate) that persist for weeks or months. This persistent reactive distress is not adaptive and frequently requires psychiatric treatment. These disorders are classified in the current *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV)* (7) as adjustment disorders with depressed mood, anxiety, or mixed anxiety and depressed mood, depending on the major symptoms. For these patients, mental health professionals working in oncology use short-term supportive psychotherapy based on a crisis intervention model. This approach offers emotional support, provides information to help the patient adapt to the crisis, emphasizes past strengths, and supports previously successful ways of coping. Patients and their families are seen at least weekly, and anxiolytic or antide-pressant drugs are prescribed as indicated. As symptoms improve, medication can be reduced and discontinued. Having the patient talk with another patient who has been through the same treatment is often a helpful adjunct (8).

PREVALENCE OF PSYCHIATRIC DISORDERS IN PATIENTS WITH CANCER

There are many myths about the psychological problems of patients with life-threatening illness, the conclusions of which range from “all patients are distressed and need psychiatric help” to “none is upset and no one needs help.” One of the first efforts in the field of psychooncology was to obtain objective data on the type and frequency of psychological problems in cancer patients. These data are useful to plan for the provision of services and use of support staff in cancer centers and oncology units.

Using criteria from the *DSM-III* (9) classification of psychiatric disorders, the Psychosocial Collaborative Oncology Group (PSYCOG) determined the psychiatric disorders in 215 randomly selected hospitalized and ambulatory adult cancer patients in three cancer centers (10). Slightly over half (53%) of the patients evaluated were adjusting normally to stress; the remainder (47%) had clinically apparent psychiatric disorders. Of the 47% with psychiatric disorders, over two-thirds (68%) had reactive or situational anxiety and depression (adjustment disorders with depressed or anxious mood), 13% had a major depression, 8% had an organic mental disorder, 7% had a personality disorder, and 4% had a preexisting anxiety disorder. Thus, nearly 90% of the psychiatric disorders observed in this study were reactions to, or manifestations of, disease or treatment. Only 11% represented prior psychiatric problems, such as personality disorders or anxiety disorders. Comparable research in children is lacking, but clinical data appear to reflect a similar spectrum of problems. The physician who treats patients with cancer can expect, for the most part, to find a group of psychologically healthy individuals who are responding to the stresses posed by cancer and its treatment with symptoms that can be relieved with the short-term use of medication.

Disorders in Cancer Patients with Pain

In the PSYCOG study (10), 39% of those who received a psychiatric diagnosis were experiencing significant pain. In contrast, only 19% of patients who did not receive a psychiatric diagnosis had significant pain. The psychiatric diagnosis of the patients with pain was predominately adjustment disorder with depressed or mixed mood (69%); however, it is of note that 15% of patients with significant pain had symptoms of major depression. In a study of cancer pain syndromes, unmanaged pain emerged as a causal factor in patient's reports of increased anxiety (11,12).

Both data and clinical observation suggest that the psychiatric symptoms of patients who are in pain must initially be considered a consequence of uncontrolled pain. Acute anxiety, depression with despair (especially when the patient believes that pain means disease progression), agitation, irritability, uncooperative behavior, anger, and inability to sleep may be the emotional or behavioral concomitants of pain. These symptoms are not labeled as a psychiatric disorder unless they persist after pain is adequately controlled. Clinicians should manage pain (13) and then reassess the patient's mental state after pain is controlled, to determine whether the patient has a psychiatric disorder.

IMPACT OF DEPRESSION AND ANXIETY ON MANAGEMENT OF PATIENTS WITH CANCER

The timely diagnosis and effective management of depression and anxiety in cancer patients contribute not only to an improvement in quality of life but also enhanced

patient involvement in oncological treatment. A meta-analysis of the effects of depression and anxiety on compliance with medical treatment suggests that depressed patients are three times more likely to be noncompliant than nondepressed patients (14). Additionally, depression may impair patients' capacity to understand and process information about their prognosis (15).

SCREENING FOR PSYCHOLOGICAL DISTRESS IN PATIENTS WITH CANCER

The presence of psychological distress can have a significant impact on patients' lives. Despite this understanding, however, in the context of a busy oncology clinic, the focus on psychological symptoms is likely not paramount. Coupled with this time pressure is the concern on the part of many patients that alerting their health care providers to their psychological distress may divert their physicians from pursuing the most aggressive cancer regimen. To address this issue, brief pencil and paper screening measures such as the Hospital Anxiety and Depression Scale, the Zung Depression Scale, or a Visual Analog Scale measuring psychological distress can rapidly identify patients whose levels of distress warrant further evaluation (16,17). Teaching oncology staff members to use brief, semistructured interviews can improve their recognition of anxiety and depressive symptoms (18).

PREVALENCE OF DEPRESSION IN PATIENTS WITH CANCER

In De Florio and Massie's review of 49 studies, the prevalence of depression in cancer patients ranged from 1% to 53% (19). Most of this variance can be attributed to the lack of standardization of methodology and diagnostic criteria. For example, in a study of 152 oncology patients, Kathol and colleagues found a 13% difference (25% versus 38%) in the prevalence of depression depending on the diagnostic system used (20,21).

Using both *DSM-III* criteria, which were modified to eliminate physical symptoms characteristic of cancer, and validated depression rating scales, Bukberg and colleagues found a 42% (24% severe, 18% moderate) prevalence of depression among 62 (30 female, 32 male) patients hospitalized on oncology units (22), and Plumb and Holland found a 33% prevalence of depression among 80 (40 female, 40 male) hospitalized patients with advanced cancer (23). The Bukberg et al. finding of 42% prevalence of depression approximates the Kathol et al. finding of 38%, using the *DSM-III* criteria.

The existing data can answer many of the questions commonly asked about the prevalence of depression in patients with cancer: (a) Are there gender differences? (b) Are hospitalized patients more depressed than ambulatory patients? (c) Are those with advanced disease more depressed? In the aforementioned review of 49 studies (19), 29 included both males and females. Six studies did not examine or report gender differences, and the remaining 23 found no significant gender differences in the prevalence of depression.

Many clinicians believe that hospitalized patients with advanced cancer are more depressed than ambulatory patients. However, as more studies have been done over time, hospitalization status explains little of the large variance. Now, because of insurance restrictions, many seriously ill cancer patients who would have been hospitalized are treated in ambulatory settings.

Advanced disease has been correlated with a higher prevalence of depression in several studies. The reported prevalence of depression in patients with advanced cancer ranges from 23% (23) to 53% (24). Bukberg and colleagues found that greater physical disability measured by the Karnofsky Performance Status Scale was associated with depression in their study of 62 patients with cancer (22). Their 42% overall prevalence of depression reflected a range of 23%, in those with Karnofsky scores greater than 60, to 77% in those with Karnofsky scores <40.

Consultation data provide another source of information about depression in patients with cancer. At Memorial Sloan-Kettering Cancer Center, 59% of 546 consultations were requested for evaluation of depression, suicidal risk, or both (25). When the consultant's actual impressions were reviewed, depressive symptoms were by far the most common; adjustment disorders with depressed mood accounted for 54% of diagnoses, and major depression accounted for 9%. Breitbart reviewed data on 1080 consultation requests to the Psychiatry Service at the same institution and observed that evaluation of suicidal risk was the reason for referral in nearly 9% of referrals; suicide risk was found in 71 patients (6.5%) (26). One-third of the suicidal patients had a major depression, more than half had an adjustment disorder, and nearly 20% had a delirium or an organic brain syndrome.

DIAGNOSIS OF DEPRESSION IN PATIENTS WITH CANCER

The practice guidelines for depression developed both by the American Psychiatric Association (27) and the Agency for Health Care Policy and Research (28) are practical guides to the management of depression in adults. These guidelines provide an overview of depression in both physically healthy and medically ill patients.

The diagnosis of depression in physically healthy patients depends heavily on the presence of somatic symptoms, including anorexia, fatigue, insomnia, and weight loss. These indicators are of little value as diagnostic criteria for depression in cancer patients, as they are common to both cancer and depression. In cancer patients, the diagnosis of depression must depend on psychological, not somatic, symptoms. These psychological symptoms are dysphoric mood, feelings of helplessness and hopelessness, loss of self-esteem, feelings of worthlessness or guilt, anhedonia, and thoughts of death or suicide (29).

Mood Disorder Due to Cancer, Other Medical Conditions, or Substances

When evaluating depressed patients, it is imperative to determine whether organic factors underlie the depressive syndrome. A depressive syndrome caused by the direct physiological effects of cancer is called “mood disorder due to cancer” in the current *DSM-IV* nosology. Although the key feature of this disorder is a prominent and persistent depressed mood that resembles a major depression, the presence of encephalopathy precludes the diagnosis of mood disorder due to cancer unless depression had been diagnosed before confusional symptoms developed. The patient with a delirium due to cancer may have mild cognitive deficits, such as poor memory or decreased concentration, and may have decreased control over sexual or aggressive impulses. Tumor involvement of the central nervous system, metabolic disturbances, and the presumed organic processes associated with carcinoma of the pancreas may cause this disorder. The case of pancreatic carcinoma represents a special problem because it is often unclear whether depressive symptoms are due to an indirect effect of the cancer on the brain (possibly alteration of serotonergic function) or to a psychological reaction to this devastating cancer (30).

Among the metabolic causes of mood disorder due to cancer are electrolyte disturbances (e.g., hypercalcemia), endocrinopathies (e.g., hypothyroidism), and nutritional disorders (e.g., vitamin B12 deficiency). Infections may also be responsible (e.g., Epstein-Barr virus infection) (29).

DSM-IV defines disturbances in mood due to the direct physiological effects of a substance (i.e., a drug of abuse or a medication) as a “substance-induced mood disorder.” This diagnosis would be appropriate when depression is related to drug therapy such as b-adrenergic antagonists (31) (Table 40-1) or anticancer drugs, particularly corticosteroids, vinblastine sulfate, vincristine sulfate, procarbazine hydrochloride, asparaginase (32), tamoxifen citrate (33), or interferon (32) (Table 40-2).

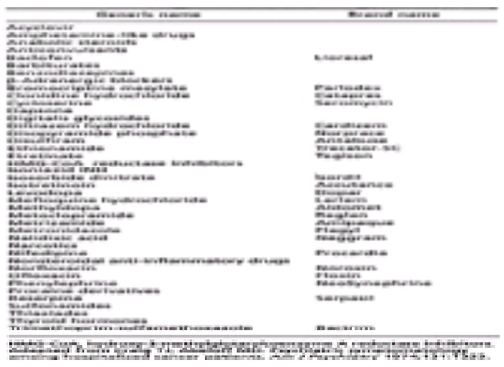

TABLE 40-1. DRUGS ASSOCIATED WITH DEPRESSIVE SYMPTOMS

Drug	Cancer
Corticosteroids	
Vinblastine sulfate	Breast, lung
Vincristine sulfate	All, brain
Interferon	Renal, Kaposi's sarcoma
Procarbazine hydrochloride	Brain
Asparaginase	All
Tamoxifen citrate	Breast
Cyproterone	Prostate

Adapted from Massie MJ, Holland JC. Consultation and liaison issues in cancer care. *Psychiatr Med* 1987;5:343.

TABLE 40-2. ANTICANCER DRUGS ASSOCIATED WITH DEPRESSION

In the medically ill, the evaluation of every depressed patient must include a thorough medical, endocrinologic, and neurological assessment. A cognitive evaluation must be performed. Many clinicians prefer to use at least one easily reproducible instrument (e.g., the Mini-Mental State Examination) (34) to document mental status at the time of the initial evaluation and subsequent evaluations. All such brief instruments have limitations because they assess only selected aspects of cognition.

If the depressive disorder is believed to be caused by a medical condition or by a drug, the clinician should first attempt to treat the disorder or change the drug. Often, antidepressants are started concurrently in an effort to alleviate symptoms more quickly or because the clinician anticipates that the depression that complicates the underlying disorder will not be relieved by addressing the medical condition alone. When the primary cause of the depression cannot be corrected (e.g., the chemotherapeutic agent must be continued), antidepressant therapy is also initiated.

Depression with Psychotic Features

Although rare, depression accompanied by delusions, hallucinations, or grossly disorganized behavior is sometimes encountered in medically ill patients. In this population, the presence of depressive symptoms (e.g., flat affect, lack of interest in daily activities) coupled with psychotic symptoms more often reflects a delirium, and before the diagnosis of depression with psychotic features is made, the presence of underlying organic causes for these mental status changes should be explored. When psychotic features are present, an antipsychotic and an antidepressant are usually started concurrently. High-potency neuroleptics (e.g., haloperidol, olanzapine, and risperidone) are usually preferred because of their low anticholinergic potential, which reduces the risk of delirium and other anticholinergic side effects (e.g., cardiac arrhythmias, constipation, urinary retention, and blurred vision). These high-potency neuroleptics also lower seizure threshold less than low-potency neuroleptics (e.g., chlorpromazine and thioridazine) and are preferable when the risk of seizures is a concern. Molindone hydrochloride, an intermediate-potency neuroleptic, has been reported to have the lowest epileptogenic potential and may also be a good choice for a patient with psychotic symptoms and seizures that are difficult to control with anticonvulsants (35).

Depression in the Elderly

Older individuals are at greater risk for depression and suicidal acts, whether physically healthy or not. In addition to the loss of good health, the elderly cancer patient often has sustained other losses, including physical ability (e.g., hearing loss) and financial stability. Grief after the death of a spouse or friends may be unresolved, and self-esteem may be damaged through retirement or changed social standing. Although the clinical presentation of depression can be similar to that described for younger adult patients, other presentations are more typical of this phase of life (36). For example, the chief complaints may be cognitive, such as poor memory or concentration. By taking a thorough history and by interviewing relatives or friends to document the patient's history, the clinician learns that depressive features may antedate the cognitive complaints. When asked specific questions, the patient often says “I don't know” instead of attempting to answer. Objective testing (e.g., with the Mini-Mental State Examination) often reveals better results than those expected based on subjective complaints. This constellation is typical of the clinical syndrome *depressive pseudodementia* and often responds well to treatment with antidepressants.

Suicide

Suicidal ideation requires careful assessment to determine whether the patient has a depressive illness or is expressing a wish to have ultimate control over intolerable symptoms. Thoughtful clinical judgment is required to make this differentiation, especially in the patient with advanced disease. Breitbart (26) has outlined factors that place a cancer patient at a high risk for suicide as follows: poor prognosis and advanced illness; depression and hopelessness; uncontrolled pain; delirium; prior psychiatric history; history of previous suicide attempts or family history of suicide; history of recent death of friends or spouse; history of alcohol abuse; and few social supports. Other risk factors include male sex; advanced age (sixth and seventh decades); presence of fatigue; and oral, pharyngeal, lung, gastrointestinal, urogenital, and breast cancers (Table 40-3).

Related to mental status
Suicidal ideations
Lethal plans (hoarding medications)
Depression and hopelessness
Delirium and disinhibition
Psychotic features (hallucinations and delusions)
Loss of control and impulsivity
Irrational thinking
Related to cancer
Uncontrolled pain
Advanced disease and poor prognosis
Site (oral pharyngeal, lung, gastrointestinal, urogenital, breast)
Exhaustion and fatigue
Medication effects (steroids)
Related to history
Prior suicidal attempts
Psychopathology
Substance abuse (alcohol)
Recent loss (spouse or friends)
Poor social support
Older male
Family history of suicide

TABLE 40-3. SUICIDE RISK FACTORS IN CANCER PATIENTS

Cancer patients have twice the risk of actually committing suicide as the general population (37,38 and 39). Many factors, such as poor prognosis, delirium, uncontrolled pain, depression, and hopelessness, are often linked in a patient with advanced disease, together increasing the risk of suicide. Hopelessness is an even stronger predictive factor than depression itself (40). Cancer patients usually commit suicide by overdose with analgesics or sedative drugs prescribed by their doctors. Men use violent means, such as hanging or gunshot, more often than women.

The management of the suicidal cancer patient includes maintaining a supportive therapeutic relationship; conveying the attitude that much can be done to improve the quality, if not the quantity, of life even if the prognosis is poor; and actively eliciting and treating specific symptoms (e.g., pain, nausea, insomnia, anxiety, and depression). The most useful psychotherapeutic modalities are based on a crisis intervention model using cognitive techniques (e.g., giving back a sense of control by helping the patient to focus on that which can still be controlled) and supportive methods, usually involving family and friends. One should keep in mind that the spouse and other family members are also at increased risk for suicide and that they also often require evaluation and support (1).

At Memorial Sloan-Kettering Cancer Center, virtually all hospitalized patients who have attempted suicide have had poorly controlled pain, mild encephalopathy, disinhibition secondary to drugs, and hopelessness combined with distress about the inability to communicate their concerns about their discomfort to caregivers. If a patient is suicidal, a 24-hour companion is provided to establish constant observation, monitor the suicidal risk, and reassure the patient. Need for observation is evaluated daily; companions are discontinued when the patient is no longer suicidal and is judged to be in control and able to act rationally.

TREATMENT OF DEPRESSION

Before planning an intervention, the patient should be evaluated for a history of previous depressive episodes and substance (including alcohol and cocaine) abuse, family history of depression and suicide, concurrent life stresses, losses secondary to cancer (e.g., financial, social, and occupational), and the availability of social

support. An assessment of the meaning of illness to the patient and his or her understanding of the medical situation (including prognosis) is essential. Depressed patients with cancer are usually treated with a combination of supportive psychotherapy and antidepressants (8,29); electroconvulsive therapy (ECT) is used less often.

Psychological Treatment

The goals of psychotherapy are to reduce emotional distress and to improve morale, coping ability, self-esteem, sense of control, and resolution of problems (41). Cancer patients are often referred for, or request, psychiatric consultation at times of crisis in illness—at the time of diagnosis or diagnosis of recurrence, at the beginning of any new treatment, when standard or experimental treatments fail, or when patients perceive themselves as dying. The referral is often an emergency and, because of the acute crisis, the patient often readily accepts an intervention.

Various models of intervention for the acutely or chronically medically ill have been described, including timelimited dynamic psychotherapy, short-term dynamic therapy (42), and cognitive-behavioral therapy (43). Often, 4–15 sessions are required to treat the acute problem. The patient considers his or her recent losses (good health, body integrity, self-esteem, family support, presumed longevity, financial security, and opportunity for job satisfaction) in the context of a past history of loss or success, and is helped to chart a future direction that incorporates life and body alterations brought on by the diagnosis of a chronic lifethreatening illness. As mentioned above, the most useful model is based on a crisis intervention model that involves an active therapeutic role.

Brief psychoeducation interventions that orient patients and family members to the oncological setting and provide opportunities for questions can lead to reductions in anxiety and depression (44). Educational interventions, such as clarifying information and explaining emotional reactions to the patient, family, and staff, are useful. Cognitive techniques are also useful to help the patient correct misconceptions and exaggerated fears. Patients are encouraged to consider an array of different possible explanations or outcomes for their situation and then to determine which aspects they can still improve. This approach provides the patient with a sense of control over his or her situation and helps the individual to avoid focusing only on the worst eventualities.

Emotional support is also provided. Listening to the patient carefully and allowing him or her to express feelings, fears, and anger in a nonjudgmental setting is often therapeutic. Legitimization of the difficulty of the situation and of the right to be upset reduces the fear of being perceived as weak or inappropriate. Reassurances should be realistic and consistent with the available knowledge of the situation. The desire of patients to maintain hope is, of course, respected, as are the defense mechanisms of denial, repression, and regression, as long as these do not interfere with diagnostic or therapeutic processes or with important personal matters that must be addressed. As the patient's history of loss is explored, the clinician identifies and reinforces his or her successful ways of coping. At the termination of psychotherapy, patients are reassured to hear that the clinician is available for future visits if symptoms recur or if the disease worsens (1).

Another important aspect of the treatment of the depressed cancer patient is social support provided by family, friends, and community or religious groups. Although family is enlisted to provide emotional support, family members must be encouraged to minimize family conflicts, which add an additional emotional burden and can be addressed more appropriately after the depression has resolved. This process may also identify vulnerable family members who cannot provide emotional support and indeed may also need psychosocial help. These family members are encouraged to seek individual or group support for themselves.

Drug Therapies

Antidepressants

Although there are many reports of the efficacy of antidepressants in depressed patients with cancer (45,46 and 47), there is only one double-blind, placebo-controlled study (48) demonstrating efficacy. This observation reflects the difficulty in conducting controlled studies of drugs in medically ill cancer patients. Nonetheless, there is much clinical experience with antidepressant drugs in this population. The antidepressant agents that can be considered for use in cancer patients are (a) the newer agents, including selective serotonin reuptake inhibitors (SSRIs); (b) tricyclic antidepressants (TCAs); (c) psychostimulants; (d) lithium carbonate; and (e) the monoamine oxidase inhibitors (MAOIs) (49) (Table 40-4).

Drug	Starting daily dosage, mg (p.o.)	Therapeutic daily dosage, mg (p.o.)
Newer agents		
Serotonin reuptake inhibitors		
Fluoxetine hydrochloride	20	20–60
Sertraline hydrochloride	50	50–150
Paroxetine hydrochloride	10	10–50
Citalopram hydrobromide	10	10–50
Others		
Amoxapine	25	100–150
Maprotiline hydrochloride	25	75–150
Trazodone hydrochloride	50	150–300
Bupropion hydrochloride	75	200–300
Venlafaxine hydrochloride	18.75	75–225
Nefazodone hydrochloride	50	50–300
Mirtazapine	15	15–45
Tricyclic antidepressants		
Amitriptyline hydrochloride	25	50–150
Doxepin hydrochloride	25	50–200
Imipramine hydrochloride	25	50–200
Desipramine hydrochloride	25	50–150
Nortriptyline hydrochloride	25	50–150
Protriptyline hydrochloride	20	10–30
Psychostimulants		
Dextroamphetamine	2.5 at 8 a.m. and noon	5–30
Methylphenidate hydrochloride	2.5 at 8 a.m. and noon	5–30
Pemoline	18.75 at a.m. and at noon	37.5–150
Monoamine oxidase inhibitors		
Isocarboxazide	10	20–40
Phenelzine sulfate	15	60–90
Tranylcypromine sulfate	10	20–60
Lithium carbonate	300	600–1200
Benzodiazepine		
Alprazolam	0.25–1.00	0.75–4.00

TABLE 40-4. ANTIDEPRESSANT MEDICATIONS USED IN CANCER PATIENTS

Newer Antidepressants

The SSRIs fluoxetine hydrochloride, sertraline hydrochloride, paroxetine hydrochloride, and citalopram hydrobromide are often prescribed first because they have fewer sedative and autonomic effects than TCAs. The most common side effects are nausea, headache, somnolence or insomnia, and a brief period of increased anxiety; hyponatremia is an uncommon adverse effect (50). These drugs can cause appetite suppression that usually lasts a period of several weeks, but the anorectic properties of these drugs have not been a limiting factor in this population. Paroxetine hydrochloride has no active metabolites, and sertraline hydrochloride has fewer than fluoxetine hydrochloride; both have a shorter half-life than fluoxetine hydrochloride. Their characteristics reduce the risk of accumulation during dose finding and allow more precise titration. Paroxetine hydrochloride has demonstrated effectiveness in the management of depression in patients with malignant melanoma receiving high-dose interferon-a (51).

Bupropion hydrochloride, trazodone hydrochloride, maprotiline hydrochloride, amoxapine, venlafaxine hydrochloride, nefazodone hydrochloride, and mirtazapine are prescribed less frequently than the SSRIs. Bupropion hydrochloride is considered if patients have a poor response to a reasonable trial of other antidepressants. It may be somewhat activating in medically ill patients and should be avoided in patients with seizure disorders, brain tumor, other factors that predispose to seizures, or malnutrition. Trazodone hydrochloride is strongly sedating and in low doses (100 mg at bedtime) is helpful in the treatment of the depressed cancer patient with insomnia. Effective antidepressant doses are often greater than 300 mg/day. Trazodone hydrochloride has been associated with priapism and should therefore be used with caution in men. Maprotiline hydrochloride should be avoided in patients at high risk for seizures. Amoxapine has strong dopamine-blocking activity; hence, patients taking other dopamine blockers (e.g., antiemetics) have an increased risk of developing extrapyramidal symptoms and dyskinesias. Venlafaxine hydrochloride is a selective inhibitor of uptake pumps for both serotonin and norepinephrine. In addition to antidepressant effects, venlafaxine hydrochloride, along with many of the SSRIs, is useful in the management of autonomic instability hot flashes in women with chemotherapy-induced menopausal symptoms. Nefazodone hydrochloride is structurally similar to trazodone hydrochloride and requires a twice-a-day dosing schedule. Mirtazapine does not block the reuptake of neurotransmitters but rather acts as an antagonist that increases noradrenergic and serotonergic activity. In low doses it is effective for treatment of insomnia and loss of appetite; in higher doses it is more activating and has greater antidepressant effects. Additionally, it may have antiemetic effects (52).

When treating depression in the elderly, medications are started at a low dose, and the dosage is increased more slowly than with a younger adult patient. Also, drugs with few anticholinergic effects are preferred due to greater sensitivity of the elderly to anticholinergic complications (e.g., delirium, urinary retention, and cardiac arrhythmias) (53).

The use of herbal supplements has increased in the population in general and in patients with cancer specifically. Many of these supplements (e.g., kava, valerian, St. John's wort, hops, lemon balm, and SAM-e) have potential interactions with psychotropic medications. For example, kava interacts with benzodiazepines; St. John's wort and SAM-e interact with antidepressants; and hops, valerian, and lemon balm interact with central nervous system depressants. Jenkins et al. have compiled and synthesized current understanding about the potential impact of these herbal supplements (54).

In contrast to adults, there are no clear data to support the efficacy of antidepressants in children (55). Nevertheless, clinicians often find it helpful to prescribe antidepressants to treat specific symptoms associated with depression. When the target symptoms are insomnia, poor appetite, or anxiety, a sedative TCA (e.g.,

amitriptyline hydrochloride or doxepin hydrochloride) is usually prescribed. When the clinical picture is dominated by lack of energy or motivation, an SSRI or an energizing tricyclic, such as desipramine hydrochloride, may be selected. As in the elderly, these drugs are started at a low dose.

Tricyclic Antidepressants

TCAs are still used in the oncology setting for both adults and children with cancer. Dosing is typically initiated at 10–25 mg at bedtime, especially in debilitated patients, and the dose is increased by 25 mg every 1–2 days until beneficial effect is achieved. For reasons that are unclear, depressed cancer patients often show a therapeutic response to a tricyclic at much lower doses (75–125 mg daily) than are usually required in physically healthy depressed patients (150–300 mg daily). Patients are usually maintained on a TCA for 4–6 months after symptoms improve, after which time the dose is gradually lowered and discontinued (49). The effects on appetite and sleep are frequently immediate; the effects on mood may be delayed.

The choice of TCA depends on the nature of the depressive symptoms, medical status, and side effects of the specific drug. The depressed patient who is agitated and has insomnia benefits from the use of a TCA that has sedating effects, such as amitriptyline hydrochloride or doxepin hydrochloride. Patients with psychomotor slowing benefit from use of the compounds with the least sedating effects, such as protriptyline hydrochloride or desipramine hydrochloride. The patient who has stomatitis secondary to chemotherapy or radiotherapy, or who has slow intestinal motility or urinary retention, should receive a TCA with the least anticholinergic effects, such as desipramine hydrochloride or nortriptyline hydrochloride.

Patients who are unable to swallow pills may be able to take an antidepressant in an elixir (amitriptyline hydrochloride, nortriptyline hydrochloride, or doxepin hydrochloride) or in an intramuscular form (amitriptyline hydrochloride or imipramine hydrochloride). Hospital pharmacies can prepare some TCAs (e.g., amitriptyline hydrochloride) in rectal suppository form, but absorption by this route has not been studied in cancer patients. Intramuscular administration causes discomfort because of the volume of the vehicle; hence, 50 mg is usually the maximum dosage that can be delivered per intramuscular injection. Parenteral administration of TCAs may be considered for the cancer patient who is unable to tolerate oral administration because of impaired swallowing, the presence of gastric or jejunal drainage tubes, or intestinal obstruction. Although three TCAs (amitriptyline hydrochloride, imipramine hydrochloride, and clomipramine hydrochloride) are available in injectable form, the U.S. Food and Drug Administration has approved imipramine hydrochloride and amitriptyline hydrochloride for oral and muscular administration and clomipramine hydrochloride for oral use only. Formal informed consent and close monitoring of the electrocardiogram is recommended when these medications are used intravenously.

Imipramine hydrochloride, doxepin hydrochloride, amitriptyline hydrochloride, desipramine hydrochloride, and nortriptyline hydrochloride are used frequently in the management of neuropathic pain in cancer patients. Dosing is similar to that in the treatment of depression. Analgesic efficacy, if it occurs, is usually observed at a dose of 50–150 mg daily; higher doses occasionally are needed. Although the initial assumption was that analgesic effect resulted indirectly from the effect on depression, it is now clear that these tricyclics have a separate specific analgesic action, which is probably mediated through several neurotransmitters, most prominently norepinephrine and serotonin (56).

Lithium Carbonate

Patients who have been receiving lithium carbonate for bipolar affective disorder before cancer should be maintained on it throughout cancer treatment, although close monitoring is necessary when the intake of fluids and electrolytes is restricted, such as during the preoperative and postoperative periods. The maintenance dose of lithium carbonate may need reduction in seriously ill patients. Lithium carbonate should be prescribed with caution in patients receiving cisplatin due to potential nephrotoxicity of both drugs.

Although several authors have reported that the leukocytosis produced by lithium carbonate could be beneficial in neutropenic cancer patients (57,58), the functional capabilities of these leukocytes have not been determined. The bone marrow stimulation appears to be transient. In patients without prior affective disorder, lithium carbonate does not produce mood changes.

Monoamine Oxidase Inhibitors

If a patient has responded well to an MAOI for depression before treatment for cancer, its continued use is warranted. Most psychiatrists, however, are reluctant to start depressed cancer patients on MAOIs because the need for dietary restriction is poorly received by patients who already have dietary limitations and nutritional deficiencies secondary to cancer illness and treatment.

Psychostimulants

In cancer patients, the psychostimulants (i.e., dextroamphetamine, methylphenidate hydrochloride, and pemoline) promote a sense of well-being, decrease fatigue, and stimulate appetite (59,60). An advantage of these drugs is a rapid onset of antidepressant action compared with that of the TCAs. Psychostimulants can potentiate the analgesic effects of opioid analgesics and are commonly used to counteract opioid-induced sedation (61). Occasionally they can produce nightmares, insomnia, and even psychosis.

Treatment with dextroamphetamine and methylphenidate hydrochloride is usually initiated at a dose of 2.5 mg at 8 a.m. and noon. Pemoline, a chewable and less potent psychostimulant, is usually initiated at a dose of 18.75 mg at 8 a.m. The dose and dosing interval should be adjusted to optimize effects. Typically, patients are maintained on a psychostimulant for 1–2 months, after which time approximately two-thirds are able to be withdrawn without a recurrence of depressive symptoms (62). Those who develop recurrence of depressive symptoms can be maintained for long periods (e.g., >1 year). Tolerance may develop, requiring dose adjustments. Pemoline should be used with caution in patients with renal impairment; liver function tests should be monitored periodically with longterm treatment (63).

Electroconvulsive Therapy

ECT is indicated for medically ill patients who are depressed and are refractory to antidepressants, or have depression with psychotic or dangerously suicidal features. Patients who have significant contraindications to treatment with antidepressant drugs are also considered for this approach. The safe and effective use of ECT in the medically ill has been reviewed by others (64).

PREVALENCE OF ANXIETY IN PATIENTS WITH CANCER

Cancer disrupts the social roles of patients, their interpersonal relationships, and the ways in which they view their future (65); most people who have cancer are both fearful and sad. In the general population, anxiety is associated with female gender, younger age, and lower socioeconomic status (66). These patterns do not appear in cancer patients, suggesting that demographic factors may become less important in disease-related anxiety. Evaluation of anxiety symptoms is a frequent reason for psychiatric consultation in the oncology setting, accounting for 16% of requests in one study (25). In this study (25), 25% of patients were diagnosed as having either an anxiety disorder (4%) or an adjustment disorder with anxious mood (21%); in contrast, 57% were diagnosed as having either major depression (9%) or an adjustment disorder with depressed mood (48%). In the PSYCOG study, approximately 21% of the sample had symptoms of anxiety (10), and in several controlled studies cancer patients have been found to have higher levels of anxiety than healthy individuals. Patients with cancer are approximately twice as likely to have severe anxiety compared to controls (67,68). For example, 27% of women undergoing mastectomy had moderate to severe anxiety compared to 14% of controls, and 28% of advanced melanoma patients were anxious in comparison to 15% of controls.

Most studies of psychiatric symptoms in cancer patients have reported a higher prevalence of mixed anxiety and depressive symptoms than anxiety alone (10). Correlations between measures of depression and anxiety on both clinician-rated (69) and self-report measures (70) are high. In all likelihood, this observation indicates that these measures tap a common psychological trait: negative affect (71).

Anxiety increases with the diagnosis of cancer, peaks before surgical interventions, and frequently remains high thereafter, declining gradually during the first postoperative years (67). Others have reported that anxiety increases as cancer progresses, and psychological health declines along with the decline in physical status (70,72). Chemotherapy administration is a source of anxiety that may develop into a conditioned anticipatory response, which may persist for years after the cessation of the chemotherapy (73,74 and 75). Radiotherapy treatment is also associated with increased anxiety, accompanied by concerns about increased bodily vulnerability and worries about whether the radiation will cause further bodily damage (76). The anxiety experienced during chemotherapy and radiation therapy may paradoxically increase at the termination of treatment, as patients feel unprotected, see their physician(s) less often, and worry about the effectiveness of treatment. Patients who are participating in clinical trials and feel that they have been randomized to a less aggressive treatment modality may also experience increased anxiety (77).

DIAGNOSIS OF ANXIETY IN PATIENTS WITH CANCER

A small percentage of cancer patients have anxiety disorders that antedate the diagnosis of cancer and are exacerbated by the stress associated with cancer diagnosis or treatment (78). For most patients, anxiety symptoms are reactions to cancer and its treatment and are associated with feelings of foreboding, apprehension, or dread. Although anxiety symptoms can be either cognitive or somatic, the most salient symptoms are usually somatic and include tachycardia, shortness of breath, sweating, abdominal distress, and nausea. Loss of appetite, diminished libido, and insomnia, symptoms also associated with depression, are common in patients with anxiety, as are feelings of hyperarousal and irritability. In patients with panic attacks, symptoms related to increased autonomic discharge increase dramatically.

In addition to somatic symptoms, the anxious cancer patient is often plagued with recurrent unpleasant thoughts about cancer, including fears of death, disfigurement, disability, and dependency. The thinking style of the anxious patient is characterized by overgeneralization and catastrophizing; negative outcomes seem inevitable, and patients view themselves as helpless in a hopeless situation. Anxious patients may see their environment as threatening and often are motivated to flee, a reaction that commonly precipitates treatment refusals or demands for premature hospital discharge (78).

Phobia, Panic Disorders, Generalized Anxiety Disorder, and Posttraumatic Stress Disorder

Phobias, panic disorder, posttraumatic stress disorder (PTSD), and generalized anxiety disorder may antedate the diagnosis of cancer or first appear as patients are diagnosed and undergo cancer treatment. Because they cause extreme distress and have the potential to interfere with adequate medical management, it is important to accurately diagnose and treat these anxiety disorders (79).

There is a range of phobias that can be exacerbated by exposure to the medical environment—phobias about needles, blood, hospitals, and doctors are common. The common characteristic of all phobias is extreme anxiety on exposure to a feared object(s) or situation(s), and a persistent anxiety in the anticipation of these situations. Agoraphobia (the most common phobia in the general population) and claustrophobia may appear *de novo* in patients who are confined in the frightening hospital environment without their usual environmental supports. Patients who require magnetic resonance imaging or radiation therapy or who must be confined in intensive care or reverse-isolation settings frequently experience increased anxiety (80).

Although usually diagnosed before cancer, panic disorders can present in the context of a cancer diagnosis (81). In contrast to phobias, in which there is a clearly defined situation or object of dread, panic disorder often presents as sudden, unpredictable episodes of intense discomfort and fear, accompanied by shortness of breath, diaphoresis, tachycardia, feelings of choking or being smothered, and thoughts of impending doom. Symptoms of a preexisting panic disorder may intensify during cancer treatment; severe untreated symptoms may result in abrupt termination of cancer treatment. In contrast to panic disorder, generalized anxiety disorder is characterized by continuous and pervasive worry, difficulty in controlling the worry or apprehension, and the presence of symptoms of autonomic hyperactivity and hypervigilance.

In addition to heightened psychological distress associated with cancer treatment, cancer patients may experience the symptoms characteristic of PTSD after the completion of treatment. This disorder is similar to that reported by individuals who have been subjected to other types of trauma (e.g., combat, rape, or natural disaster) (82). In one study almost half (48%) of a group of cancer survivors reported symptoms related to PTSD, with 4% meeting the criteria for current PTSD diagnosis and 22% meeting the criteria for a lifetime diagnosis of PTSD (83). Patients with this disorder may repeatedly reexperience frightening events associated with their cancer diagnosis or treatment and have a chronic exaggerated startle response, nightmares, or autonomic hyperactivity.

Anxiety Disorder Due to Cancer, Other Medical Conditions, or Substances

Anxiety in cancer patients may be caused or exacerbated by medications used to treat cancer or other conditions, abnormal metabolic states, or uncontrolled pain. Anxiety may also be conditioned by events related to chemotherapy or radiation therapy. Although previous diagnostic nosologies did not allow for the classification of anxiety symptoms resulting from medically related causes, the *DSM-IV* (7) has included the diagnostic categories of anxiety disorder due to a medical condition (e.g., cancer) and substanceinduced anxiety disorder.

Some drugs, such as the corticosteroids, can produce anxiety, and others (e.g., neuroleptics) can cause restlessness and agitation that is described as anxiety by the patient. The akathisia produced by neuroleptics (e.g., metoclopramide and prochlorperazine), for example, is frequently misdiagnosed as anxiety (84). Drug intoxication (e.g., cocaine) and withdrawal symptoms (e.g., from alcohol, benzodiazepines, or opioids) also have anxiety as a common symptom. Bronchodilators, b-adrenergic drugs, and psychostimulants (including caffeine) can cause anxiety, irritability, and tremulousness. Thyroid replacement medication can produce symptoms of anxiety, especially when the dosage is being adjusted (85).

Metabolic disturbances such as hypoglycemia, hypoxia, and undetected anemia may be manifested by symptoms of anxiety, restlessness, and agitation, followed by confusion and disorientation. Encephalopathy associated with systemic infection and the remote effects of specific tumors (pancreatic [86], thyroid [87], pheochromocytomas [88], and parathyroid [89]) may also result in high levels of anxiety. Some patients with central nervous system neoplasms report anxiety as a prominent symptom (90).

Chemotherapy and radiation therapy can be associated with increased anxiety. Repeated exposures to highly emetogenic chemotherapeutic agents may lead to the development of anticipatory nausea and vomiting (ANV), a conditioned response to environmental cues (e.g., the sight of the hospital or the smell of the alcohol swabs) that surround the chemotherapy experience. There is evidence that ANV may be linked to a preexisting anxiety diathesis and may persist for years after the cessation of chemotherapy (75,91). Patients undergoing radiation therapy may experience a level of apprehension and anxiety that may persist as treatment progresses (92). Worsening side effects and the fear associated with the cessation of treatment may perpetuate the anxiety. The psychological distress associated with radiation therapy may exceed the physical distress resulting from the treatment itself (93,94 and 95).

Anxiety as a Manifestation of Other Psychiatric Disorders

In the medically ill, anxiety may be a manifestation of either depression or delirium. Increasingly, depression and anxiety are viewed as syndromes existing on a continuum; there is an overlap in the symptomatology between these two mood states. Depression may be distinguished from anxiety by the presence of the psychological symptoms such as hopelessness, anhedonia, worthlessness, and suicidal ideation. Delirium frequently has anxiety or restlessness as a prominent feature but is distinguished from anxiety by the presence of disorientation, impaired memory and concentration, fluctuating level of consciousness, and altered perceptions, including hallucinations and delusions (96).

TREATMENT OF ANXIETY

The most effective management of anxiety in cancer patients is multimodal, including psychotherapy, behavioral therapy, and pharmacological management. During the initial evaluation of the patient's symptoms, both emotional support and information are given to the patient (97). Exploration of the patient's fears and apprehensions about disease progression, upcoming procedures, or psychosocial concerns often alleviates a substantial degree of the anxiety. Patient concerns usually include death, physical suffering, increased dependence, changes in social role functioning, spiritual matters, and worry about finances or employment (98).

Psychological Treatment

Relatively short-term psychological interventions have proven to be effective in reducing the distress associated with cancer (99). The efficacy of psychological treatments without the use of drugs depends on the duration and severity of the patient's anxiety. In the case of mild to moderate anxiety, the use of psychological techniques alone may be sufficient (100). In addition to effectively treating distress in patients presenting with anxiety, a meta-analysis of psychological interventions suggests that these interventions, such as cognitive-behavioral techniques, can effectively prophylax against the development of anxiety in patients diagnosed with cancer (101).

Careful patient selection is important for the success of psychological approaches. Cancer patients most likely to benefit from psychological interventions are those who have anxiety that has not been controlled by other means, have a need for self-control and are reluctant to take medication, and have experienced or acknowledge the efficacy of such approaches. Individuals who are poor candidates for psychological approaches are those who have delirium or dementia, are disinterested or demonstrate noncompliance in learning to use psychological techniques, and have a history of serious psychiatric illness (102).

The psychological interventions for anxiety in cancer patients comprise four categories: psychoeducational, behavioral, cognitive-behavioral, and group interventions (103). In general, the most effective treatment programs for anxiety involve a treatment package that includes a variety of behavioral, cognitive-behavioral, and psychoeducational techniques (104).

Psychoeducational interventions are particularly useful for anxious cancer patients who have difficulty understanding medical information about their prognosis and

planned procedures and treatments. As patients begin surgical, chemotherapeutic, or radiotherapeutic interventions, providing information about predictable side effects helps to normalize the experience and reduce anxiety (105,106). Similarly, explaining the predictable emotional phases associated with cancer may alleviate anxiety. Providing information to a patient's family can improve the coping of family members, which in turn enhances the patient's sense of support (2,107).

The rationale for the use of behavioral techniques, including relaxation training, guided imagery, or hypnotherapy, is the substitution of more adaptive behavior (e.g., increased coping ability) for less adaptive behavior (e.g., anxiety). Progressive relaxation involves instructing the patient to sequentially relax parts of the body through either tensing and relaxing the muscle groups (active muscle relaxation) or through concentrating on relaxing parts of the body without tensing the muscles (passive muscle relaxation). Both approaches are effective in reducing anxiety, although in medically debilitated patients passive relaxation may be more manageable (108). Relaxation has been demonstrated to be effective in the management of anxiety in cancer patients, and when compared to alprazolam, relaxation was found to be only slightly less effective (109,110 and 111). Guided imagery is a component of a progressive relaxation training program, and a behavioral treatment that includes both guided imagery and relaxation has been demonstrated to be more effective in lowering distress than either component alone (112,113). Hypnosis can be effective in the management of psychological distress associated with procedures (114) and in the management of treatment-related side effects such as ANV and pain. Desensitization, response prevention, thought stopping, modeling, and distraction are other behavioral techniques that may be useful in the management of anxiety and phobias (102).

Behavioral techniques have also been demonstrated to be effective in the treatment of ANV. As noted previously, ANV appears to be correlated with preexisting trait anxiety (91) and with state anxiety at the time of the chemotherapy infusions (115). Progressive muscle relaxation has been shown to decrease nausea and vomiting, as well as anxiety, in patients who are receiving emetogenic chemotherapy (109,112,116). An approach to ANV that combines behavioral approaches and a cognitive approach in which the patient's thoughts and feelings about chemotherapy are explored and modified may be most effective (117).

Individual psychotherapy (103), including cognitivebehavioral approaches (118), can be effective in the treatment of cancer-related anxiety. According to the cognitivebehavioral model, emotional distress arises or continues because of maladaptive beliefs and thinking patterns. Patients are encouraged to identify these maladaptive thoughts, reconsider them more logically, and experiment with alternative viewpoints and behaviors that give them greater control over their situation. Adjuvant psychological therapy is a structured cognitive-behavioral intervention that teaches patients to identify negative thoughts, rehearse impending stressful events, implement ways of handling them more effectively, plan and carry out practical activities that create a sense of mastery, express feelings openly to one's partner, and increase both self-esteem and a fighting spirit by identifying and fostering personal strengths (119). Follow-up studies of this intervention have consistently demonstrated significantly lower scores on anxiety and psychological distress as compared to controls (119,120). When compared to nondirective supportive counseling, adjuvant psychological therapy produced greater reductions in levels of anxiety in cancer patients (121).

Group interventions have also been shown to reduce psychological distress in cancer patients (103). These interventions have benefited patients with a variety of cancer diagnoses (122) and stages of cancer (123). In one study, patients who participated in support groups for at least a year reported less tension than did controls (123). The techniques employed in these groups included fostering a sense of supportive commonality among the members, education, emotional support, stress management, coping strategies, and behavioral training.

Pharmacological Treatment

Although a significant percentage of patients with advanced cancer receive antianxiety drugs (124), the severity of symptoms is the most useful guide in deciding whether a pharmacological approach to the management of anxiety should be tried. Patients with mild reactive anxiety may benefit from either supportive measures or behavioral measures alone.

For patients who experience persistent apprehension and anxiety, the first-line drugs are the benzodiazepines (Table 40-5). Lorazepam (0.25–2.00 mg four times daily) and alprazolam [0.25–1.00 mg t.i.d. (three times daily)] are useful for anxiety and other indications, such as nausea (lorazepam) and panic (alprazolam). Both lorazepam and alprazolam have been shown in controlled trials to reduce postchemotherapy nausea and vomiting, as well as ANV (125,126). Lorazepam also has amnestic properties; when given before chemotherapy or a procedure, this effect may reduce the likelihood that a conditioned aversion will develop (127). A longer-acting benzodiazepine, such as clonazepam (0.5–1.0 mg twice daily), may provide more consistent relief of anxiety symptoms and have mood-stabilizing effects as well. For insomnia, the benzodiazepines temazepam (15–30 mg qhs) and triazolam (0.25–0.50 mg qhs), as well as the non-benzodiazepine hypnotics zolpidem tartrate (10–20 mg qhs) and zaleplon (10 mg qhs), may be effective. Nonsedating neuroleptics such as haloperidol (5 mg qhs) or olanzapine (2.5–5.0 mg qhs) may be more effective for the patient who is both anxious and confused. For patients with compromised hepatic function, the use of shorter-acting benzodiazepines, such as lorazepam, oxazepam, and temazepam, is preferred; these drugs are metabolized by conjugation with glucuronic acid and have no active metabolites.

Drug	Approximate dose equivalent	Starting daily dose, mg (p.o.)	Absorption	Metabolites
Benzodiazepines				
Alprazolam	0.5	0.25–1.00 t.i.d.	Intermediate	Yes
Diazepam	10	10–15 t.i.d.	Slow/intermediate	No
Lorazepam	1	0.5–2.0 t.i.d.	Intermediate	No
Chlordiazepoxide	10	10–25 t.i.d.	Intermediate	Yes
Diazepam	5	2.0–10 b.i.d.	Fast	Yes
Clorazepate	7.5	7.5–15.0 b.i.d.	Fast	Yes
Clonazepam	0.25	0.25–1.00 b.i.d.	Intermediate	Yes
Temazepam	30	15–30 qhs	Intermediate	No
Triazolam	0.25	0.25–0.50 qhs	Intermediate	No
Antihistamines				
Hydroxyzine	10	10–50 t.i.d.		
Diphenhydramine hydrochloride	25	25–50 t.i.d.		
Neuroleptics				
Haloperidol	0.5	0.5–2.0 b.i.d.		
Thioridazine	10	10–50 t.i.d.		
Olanzapine	5			
Other				
Zolpidem tartrate	10	10–20 qhs		

b.i.d., twice daily; qhs, at bedtime; t.i.d., three times daily.

TABLE 40-5. ANTIANXIETY MEDICATIONS USED IN CANCER PATIENTS

Drowsiness and somnolence are the most common adverse effects of benzodiazapines. Reductions in dose and the passage of time eliminate these effects. Mental status changes, such as impaired concentration, memory, or delirium, may result from benzodiazepine usage and are more common in elderly patients, those with advanced disease, and those with impaired hepatic function.

Structurally unlike other anxiolytics, buspirone hydrochloride (5–20 mg t.i.d.) is useful for patients with generalized anxiety disorder as well as those in whom there is the potential for benzodiazepine abuse. Buspirone hydrochloride is not effective on an as-needed basis; its effects are not apparent for 1–2 weeks. Additionally, patients who have been prescribed benzodiazepines in the past may find that buspirone hydrochloride does not alleviate their anxiety as effectively as benzodiazepines.

For the treatment of panic disorder and agoraphobia, the benzodiazepine alprazolam and antidepressant medications (TCAs, SSRIs, and MAOIs) have demonstrated effectiveness. Although alprazolam rapidly blocks panic attacks, withdrawal can be difficult after prolonged use. The TCA imipramine hydrochloride is often used for panic disorder; its anticholinergic side effects, however, are not well tolerated by debilitated cancer patients. In the oncology setting, the SSRIs sertraline hydrochloride and paroxetine hydrochloride, which have fewer side effects than the TCAs, are effective in the management not only of depression but also of panic disorder (128). Although MAOIs are effective in the management of panic disorder and depression, the risk of hypertensive crisis from concomitant ingestion of drugs or tyramine-containing foods make these medications less desirable for cancer patients.

In anxious patients with severely compromised pulmonary function, the use of benzodiazepines that suppress central respiratory mechanisms may be unsafe. A low dose of an antihistamine (e.g., hydroxyzine, 10–50 mg t.i.d.) can be useful for these individuals.

CONCLUSION

Depression and anxiety are common symptoms in cancer patients. These symptoms warrant evaluation and the use of pharmacological and psychosocial interventions to relieve suffering. Psychological distress should not be regarded as an unavoidable consequence of cancer.

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SUBSTANCE ABUSE ISSUES IN PALLIATIVE CARE

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In the palliative care setting, the occurrence of substance abuse poses a complex clinical challenge. Some patients have a known history of addiction to illicit drugs or prescription medications, and some seek care while active abuse is evident. In these cases, drug use must be controlled as part of a comprehensive care plan. In other cases, the challenge relates to management of less egregious aberrant drug-taking behaviors in patients without known substance use disorders. When, for example, a patient with advanced disease and pain unilaterally escalates drug doses, uses analgesics to treat other symptoms, or gives prescriptions to others, the clinician must assess the behavior, understand the implications, and plan accordingly. Thus, the problem of chemical dependency in the medically ill spans a continuum from formal psychiatric disorders to problematic behaviors in the absence of these disorders.

With the pressure of regulatory scrutiny and the duty to treat pain but contain opioid abuse or diversion, clinicians may believe that they must avoid being duped by those abusing prescription pain medications at all costs. Although the differential diagnosis of aberrant drug-related behavior is complex, clinicians who hold this view tend to simplify the clinical implications to “addiction” or “not addiction.” This is not in the best interests of either the patient or the clinician. If the fear of regulatory oversight makes practitioners feel as if they must be right—that they have to “see through” the patient's or family's denials to guard against the possibility of being duped—undertreatment and avoidance of prescribing can result. This unfortunate outcome is not demanded by existing laws or guidelines. The clinician has an obligation to be thorough, thoughtful, logically consistent, and careful (not to mention humane and caring), but not necessarily right. Clinical management can be tailored for the multiple possibilities that might be giving rise to the behaviors noted in the assessment, and asserting control over prescriptions can be accomplished without necessarily terminating the prescribing of controlled substances entirely. Although these situations defy simple solutions, knowledgeable clinicians can implement strategies that simultaneously address the need for compassionate care and management of problematic drug use.

PREVALENCE OF ILLICIT DRUG USE

Approximately one-third of the population in the United States has used illicit drugs and an estimated 6–15% have a substance use disorder of some type (1,2 and 3). As a result of this high prevalence, and the association between drug abuse and life-threatening diseases such as acquired immunodeficiency syndrome (AIDS), cirrhosis, and some types of cancer (4), problems related to abuse and addiction are encountered commonly in palliative care settings. In diverse patient populations with progressive life-threatening diseases, a remote or current history of drug abuse presents a constellation of stigmatizing physical and psychosocial issues that can both complicate the management of the underlying disease and undermine palliative therapies. Clearly, the interface between the therapeutic use of potentially abusable drugs and the abuse of these drugs is complex and must be understood to optimize palliative care.

Substance abuse appears to be very uncommon within the tertiary care population with cancer. In 1990, only 3% of inpatient and outpatient consultations performed by the Psychiatry Service at Memorial Sloan-Kettering (MSK) Cancer Center were requested for management of issues related to drug abuse. This prevalence is much lower than the prevalence of substance use disorders in society at large, in general medical populations, and in emergency medical departments (1,2,5,6 and 7). A relatively low prevalence was also reported in the Psychiatric Collaborative Oncology Group study, which assessed psychiatric diagnoses in ambulatory cancer patients from several tertiary care hospitals (6). After structured clinical interviews, fewer than 5% of 215 cancer patients met the *Diagnostic and Statistical Manual for Mental Disorders-III* criteria for a substance use disorder (8).

The relatively low prevalence of substance abuse among cancer patients treated in tertiary care hospitals may reflect institutional biases or a tendency for patient underreporting in these settings. Many drug abusers are poor, feel alienated from the health care system, may not seek care in tertiary centers, and may be disinclined to acknowledge the stigmatizing history of drug abuse. For all these reasons, the low prevalence of drug abuse in cancer centers may not be representative of the true prevalence in the cancer population overall. In support of this conclusion, a recent survey of patients admitted to a palliative care unit observed findings indicative of alcohol abuse in over 25%. Additional studies are needed to clarify the epidemiology of substance abuse and addiction in cancer patients and others with progressive medical diseases. These patients can be adequately and successfully treated only when their addiction problems are noted by staff and the patient's special needs can be addressed (9).

DEFINITIONS OF ABUSE AND ADDICTION

Both epidemiological studies and clinical management depend on an accepted, valid nomenclature for substance abuse and addiction. Unfortunately, this terminology is highly problematic. The pharmacological phenomena of tolerance and physical dependence are commonly confused with abuse and addiction, and all the definitions applied to medical patients have been developed from experience with addict populations. The clarification of this terminology is an essential step in improving the diagnosis and management of substance abuse in the palliative care setting (Table 41-1, Table 41-2).

Term	Definition
Physical dependence	Pharmacological property of some drugs defined solely by the occurrence of abstinence on abrupt dose reduction, discontinuation of dosing, or administration of an antagonist drug
Tolerance	Diminution of one or more drug effects (either favorable effects or adverse effects) caused by exposure to the drug; may be pharmacological or associative (related to learning)
Substance abuse	Use of a substance in a manner outside of sociocultural conventions; according to this definition, all use of illicit drugs is abuse and use of a licit drug in a manner not dictated by convention (e.g., according to physician's orders) is abuse
Addiction	Commonly used term that does not appear in current psychiatric nosologies but can be taken to mean the aberrant use of a substance in a manner characterized by loss of control, compulsive use, preoccupation, and continued use despite harm

TABLE 41-1. PROPOSED TERMINOLOGY OF SUBSTANCE ABUSE

TABLE 41-2. DEFINITIONS OF SUBSTANCE DEPENDENCE AND SUBSTANCE ABUSE RECOMMENDED BY *DIAGNOSTIC AND STATISTICAL MANUAL FOR MENTAL DISORDERS-IV*

Tolerance

Tolerance is a pharmacological property defined by the need for increasing doses to maintain effects (10,11). An extensive clinical experience with opioid drugs in the medical context has not confirmed that tolerance causes substantial problems (12,13). Although tolerance to a variety of opioid effects, including analgesia, can be reliably observed in animal models (14), and tolerance to nonanalgesic effects, such as respiratory depression and cognitive impairment (15), occurs routinely in the clinical setting, analgesic tolerance seldom interferes with the clinical efficacy of opioid drugs. Indeed, most patients attain stable doses associated with a favorable balance between analgesia and side effects for prolonged periods; dose escalation, when it is required, usually heralds the appearance of a progressive painful lesion (16,17,18,19,20,21 and 22). Unlike tolerance to the side effects of the opioids, clinically meaningful analgesic tolerance, which would yield the need for dose escalation to maintain analgesia in the absence of progressive disease, appears to be a rare phenomenon. Clinical observation also fails to support the conclusion that analgesic tolerance is a substantial contributor to the development of addiction.

Physical Dependence

Physical dependence is defined solely by the occurrence of an abstinence syndrome (withdrawal) after abrupt dose reduction or administration of an antagonist (10,11,23). There is great confusion among clinicians about the differences between physical dependence and addiction. Physical dependence, like tolerance, has been suggested to be a component of addiction (24,25), and the avoidance of withdrawal has been postulated to create behavioral contingencies that reinforce drug-seeking behavior (26). These speculations, however, are not supported by experience acquired during opioid therapy for chronic pain. Physical dependence does not preclude the uncomplicated discontinuation of opioids during multidisciplinary pain management of nonmalignant pain (27), and opioid therapy is routinely stopped without difficulty in the cancer patients whose pain disappears after effective antineoplastic therapy. Indirect evidence for a fundamental distinction between physical dependence and addiction is even provided by animal models of opioid selfadministration, which have demonstrated that persistent drug-taking behavior can be maintained in the absence of physical dependence (28).

Addiction

The terms *addiction* and *addict* are particularly troublesome. These labels are often inappropriately applied to describe both aberrant drug use (reminiscent of the behaviors that characterize active abusers of illicit drugs) and phenomena related to tolerance or physical dependence. The labels *addict* and *addiction* should never be used to describe patients who are only perceived to have the capacity for an abstinence syndrome. These patients must be labeled *physically dependent*. Use of the word *dependent* alone also should be discouraged, because it fosters confusion between physical dependence and psychological dependence, a component of addiction. For the same reason, the term *habituation* should not be used.

Definitions of addict and addiction must be based on the identification of drug-related behaviors that are outside of cultural or societal norms. The ability to categorize questionable behaviors (e.g., consuming a few extra doses of a prescribed opioid, particularly if this behavior was not specifically proscribed by the clinician, or using an opioid drug prescribed for pain as a nighttime hypnotic) as nonnormative presupposes that there is certainty about the parameters of normative behavior. In the area of prescription drug use, this is problematic because there are no empirical data that define these parameters. If a large proportion of patients were discovered to engage in a specific behavior, it could be normative and judgments about deviance would be influenced accordingly. This issue was recently highlighted in a pilot survey performed at MSK Cancer Center, which revealed that inpatients with cancer harbor attitudes supporting misuse of drugs in the face of symptom management problems and that women with human immunodeficiency virus (at MSK for palliative care) engage in such behaviors commonly (29). The prevalence of such behaviors and attitudes among the medically ill raises concern about their predictive validity as a marker of any diagnosis related to substance abuse. Clearly, there is a need for empirical data that illuminate the prevalence of drug-taking attitudes and behaviors in different populations of medically ill patients.

The core concepts used to define addiction may also be problematic as a result of changes induced by a progressive disease. Deterioration in physical or psychosocial functioning caused by the disease and its treatment may be difficult to separate from the morbidity associated with drug abuse. This may particularly complicate efforts to evaluate the concept of “use despite harm,” which is critical to the diagnosis of addiction. For example, the nature of questionable drug-related behaviors can be difficult to discern in the patient who develops social withdrawal or cognitive changes after brain irradiation for metastases. Even if impaired cognition is clearly related to the drugs used to treat symptoms, this outcome might only reflect a narrow therapeutic window, rather than a desire on the patient's part for these psychic effects.

Definition of Addiction in the Medically Ill

Previous definitions that include phenomena related to physical dependence or tolerance cannot be the model terminology for medically ill populations who receive potentially abusable drugs for legitimate medical purposes. A more appropriate definition of addiction notes that it is a chronic disorder characterized by “the compulsive use of a substance resulting in physical, psychological, or social harm to the user and continued use despite that harm” (30). Although this definition was developed from experience in addict populations without medical illness, it appropriately emphasizes that addiction is, fundamentally, a psychological and behavioral syndrome. Any appropriate definition of addiction must include the concepts of loss of control over drug use, compulsive drug use, and continued use despite harm.

Even appropriate definitions of addiction have limited utility, however, unless operationalized for a clinical setting. The concept of “aberrant drug-related behavior” is a useful first step in operationalizing the definitions of abuse and addiction, and recognizes the broad range of behaviors that may be considered problematic by prescribers. Although the assessment and interpretation of these behaviors can be challenging, the occurrence of aberrant behaviors signals the need to reevaluate and manage drug taking, even in the context of an appropriate medical indication for a drug (Table 41-3).

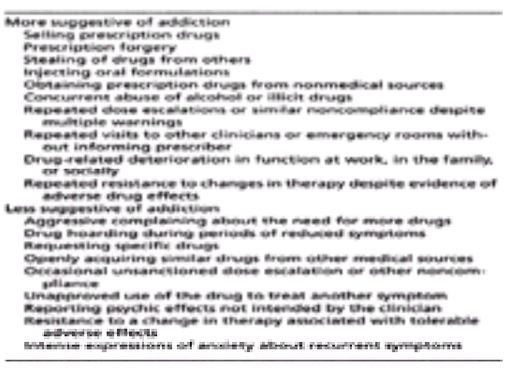

TABLE 41-3. SPECTRUM OF ABERRANT DRUG-RELATED BEHAVIORS ENCOUNTERED DURING TREATMENT OF THE MEDICALLY ILL WITH PRESCRIPTION DRUGS

If drug-taking behavior in a medical patient can be characterized as aberrant, a “differential diagnosis” for this behavior can be explored. A true addiction (substance dependence) is only one of several possible explanations. The challenging diagnosis of pseudoaddiction (74) must be considered if the patient is reporting distress associated with unrelieved symptoms. In the case of pseudoaddiction, behaviors such as aggressively complaining about the need for higher doses or occasional unilateral drug escalations indicate desperation caused by pain and disappear if pain management improves (Table 41-4).

Addiction (substance dependence disorder)
"Pseudoaddiction"
Psychiatric disorder associated with impulsive or aberrant drug taking
Personality disorders, including borderline and psychopathic personality disorders
Depressive disorder
Anxiety disorder
Encephalopathy with confusion about appropriate therapeutic regimen
Criminal intent

*Categories are not mutually exclusive.

TABLE 41-4. DIFFERENTIAL DIAGNOSIS FOR ABERRANT DRUG-RELATED BEHAVIORS[a]

Alternatively, impulsive drug use may indicate the existence of another psychiatric disorder, diagnosis of which may have therapeutic implications. Patients with borderline personality disorder can express fear and rage through aberrant drug taking and behave impulsively and self-destructively during pain therapy. Passik and Hay (31) reported a case in which one of the more worrisome aberrant drugrelated behaviors, forging of a prescription for a controlled substance, was an impulsive expression of fears of abandonment, having little to do with true substance abuse in a borderline patient. Such patients are challenging and often require firm limit setting and careful monitoring to avoid impulsive drug taking.

Similarly, patients who self-medicate anxiety, panic, depression, or even periodic dysphoria and loneliness can present as aberrant drug takers. In such instances careful diagnosis and treatment of these additional problems can at times obviate the need for such self-medication. Occasionally, aberrant drug-related behavior appears to be causally related to a mild encephalopathy, with confusion about the appropriate therapeutic regimen. This may be a concern in the treatment of the elderly patient. Low doses of neuroleptic medications, simplified drug regimens, and assistance with organizing medications can address such problems. Rarely, problematic behaviors indicate criminal intent, such as when patients report pain but intend to sell or divert medications.

These diagnoses are not mutually exclusive. A thorough psychiatric assessment is critically important, both in the population without a prior history of substance abuse and in the population of known abusers, who have a high prevalence of psychiatric comorbidity (32).

In assessing the differential diagnosis for drug-related behavior, it is useful to consider the degree of aberrancy. The less aberrant behaviors (such as aggressively complaining about the need for medications) are more likely to reflect untreated distress of some type, rather than addictionrelated concerns. Conversely, the more aberrant behaviors (such as injection of an oral formulation) are more likely to reflect true addiction. Although empirical studies are needed to validate this conceptualization, it may be a useful model when evaluating aberrant behaviors.

EMPIRICAL STUDIES USING THE ABERRANT DRUG-TAKING CONCEPT

The spectrum of the aberrant drug-taking concept has been used as a heuristic guide to the assessment of problematic drug taking in several recent studies. Although the studies performed to date all involve small samples, they have shown the usefulness of the spectrum concept as an assessment tool yielding important implications for clinicians.

The first study examined the relationship between aberrant drug-taking behaviors and compliance-related outcomes in patients with a history of substance abuse receiving chronic opioid therapy for nonmalignant pain. Dunbar and Katz (33) examined outcomes and drug taking in a sample of 20 patients with diverse histories of drug abuse who underwent a year of chronic opioid therapy. During the year of therapy, 11 patients were adherent with the drug regimen and 9 were not. The authors examined patient characteristics and aberrant drug-taking behaviors that differentiated the two groups. The patients who did not abuse the therapy were abusers of solely alcohol (or had remote histories of polysubstance abuse), were in a solid, drug-free recovery as evidenced by participation in 12-step programs, and had good social support. The patients who abused the therapy were polysubstance abusers, were not participating in 12-step programs, and had poor social support. The specific behaviors that were recorded more frequently by those who abused the therapy were unscheduled visits and multiple phone calls to the clinic, unsanctioned dose escalations, and obtaining opioids from more than one source.

A second study examined the relationship between aberrant drug taking and the presence or absence of a psychiatric diagnosis of substance use disorder in pain patients. Compton et al. (34) studied 56 patients seeking pain treatment in a multidisciplinary pain program who were referred for “problematic drug taking.” The patients all underwent structured psychiatric interviews and the sample was divided between those qualifying and those not qualifying for psychiatric diagnoses of substance use disorders. The authors then examined the subjects' reports of aberrant drug-taking behaviors in a structured interview assessment. The patients who qualified for a substance use disorder diagnosis were more likely to have engaged in unsanctioned dose escalations, received opioids from multiple sources, and have the subjective impression of loss of control of their prescribed medications.

Passik and researchers at a major cancer center (29) examined the self-reports of aberrant drug-taking attitudes and behaviors in samples of cancer (N = 52) and AIDS (N = 111) patients on a questionnaire designed for the purposes of the study. Reports of past drug use and abuse were more frequent than present reports in both groups. Current aberrant drug-related behaviors were seldom reported, but attitude items revealed that patients would consider engaging in aberrant behaviors, or would possibly excuse them in others, if pain or symptom management were inadequate. It was found that aberrant behaviors and attitudes were endorsed more frequently by the women with AIDS than by the cancer patients. Overall, patients greatly overestimated the risk of addiction during pain treatment. Experience with this questionnaire suggests that both cancer and AIDS patients respond in a forthcoming fashion to drug-taking behavior questions and describe attitudes and behaviors that may be highly relevant to the diagnosis and management of substance use disorders.

These studies help us clarify the meanings ascribed by clinicians to the various behaviors that occur during longterm administration of a potentially abusable drug. Ultimately, such studies may define the true “red flags” in a given population.

Far too often, anecdotal accounts shape the way clinicians view drug-related behaviors. Some behaviors are regarded almost universally as aberrant despite limited systematic data to suggest that this is the case. Consider for example the patient who requests a specific pain medication, or a specific route or dose. Although this behavior may reflect a patient who is knowledgeable and assertive— favorable characteristics in other contexts—it is often greeted with suspicion on the part of practitioners. Other behaviors may be common in nonaddicts, and although aberrant, they may have little predictive value for true addiction. For example, the finding that many nonaddicted cancer patients use anxiolytic medications prescribed for a friend or other (29) more than likely reflects the undertreatment and underreporting of anxiety in oncology patients than true addiction.

RISK OF ADDICTION IN THE MEDICALLY ILL

Opioid administration in cancer patients with no prior history of substance abuse is only rarely associated with the development of significant abuse or addiction (35,36,37,38,39,40,41,42,43,44,45,46 and 47). Indeed, concerns about addiction in this population are now characterized by an interesting paradox: Although the lay public and inexperienced clinicians still fear the development of addiction when opioids are used to treat cancer pain, specialists in cancer pain and palliative care widely believe that the major problem related to addiction is not the phenomenon itself, but rather the persistent undertreatment of pain driven by inappropriate fear that it will occur.

The very sanguine experience in the cancer population has contributed to a desire for a reappraisal of the risks and benefits associated with the long-term opioid treatment of chronic, nonmalignant pain (22,48). The traditional view of this therapy is negative and early surveys of addicts, which noted that a relatively large proportion began their addiction as medical patients administered opioid drugs for pain (49,50 and 51), provided some indirect support for this perspective. The most

influential of these surveys recorded a history of medical opioid use for pain in 27% of white male addicts and 1.2% of black male addicts (51).

Surveys of addict populations, however, do not provide a valid measure of the addiction liability associated with chronic opioid therapy in populations without known abuse. Prospective patient surveys are needed to define this risk accurately. Studies of relatively short-term opioid exposure have been reassuring. The Boston Collaborative Drug Surveillance Project evaluated 11,882 inpatients who had no prior history of addiction and were administered an opioid while hospitalized; only four cases of addiction could be identified subsequently (52). A national survey of burn centers could find no cases of addiction in a sample of more than 10,000 patients without prior drug abuse history who were administered opioids for pain (53), and a survey of a large headache clinic identified opioid abuse in only 3 of 2369 patients admitted for treatment, most of whom had access to opioids (54). These surveys do not define the risk of abuse or addiction during long-term, open-ended opioid therapy. They nonetheless suggest the clinical impression that patients with serious medical illness and no history of substance abuse can be given potentially abusable drugs with relatively little risk of abuse or addiction. Other supporting data derive from surveys of cancer patients and postoperative patients, which indicate that euphoria, a phenomenon believed to be common during the abuse of opioids, is extremely uncommon after administration of an opioid for pain; dysphoria is observed more typically, especially in those who receive meperidine hydrochloride (55).

The inaccurate perception that opioid therapy inherently yields a relatively high likelihood of addiction has encouraged assumptions that are not supportable given the current understanding of addiction. Perhaps most important, the relevance of a genetically determined predisposition to addiction (56) tends to be minimized or dismissed by such a view. A more critical evaluation of the extant literature (19,20,21 and 22,56,57) actually yields little substantive support for the view that large numbers of individuals with no personal or family history of abuse or addiction, no affiliation with a substance abusing subculture, and no significant premorbid psychopathology, will develop abuse or addiction *de novo* when administered potentially abusable drugs for appropriate medical indications.

ADDICTION RISK IN PATIENTS WITH CURRENT OR REMOTE DRUG ABUSE

There is very little information about the risk of abuse or addiction during, or after, the therapeutic administration of a potentially abusable drug to patients with a current or remote history of abuse or addiction. Anecdotal reports have suggested that successful long-term opioid therapy in patients with cancer pain or chronic nonmalignant pain is possible, particularly if the history of abuse or addiction is remote (33,60,61). Indeed, a recent study showed that patients with AIDS-related pain were able to be successfully treated with morphine sulfate regardless of whether they were substance users or nonusers. The major group difference found in this survey was that substance users required considerably more morphine sulfate to reach stable pain control (62).

These data are reassuring but do not obviate the need for caution. For example, although there is no empirical evidence that the use of short-acting drugs or the parenteral route is more likely to lead to problematic drug-related behaviors than other therapeutic approaches, it may be prudent to avoid such therapies in patients with histories of substance abuse.

CLINICAL MANAGEMENT

Out-of-control aberrant drug taking among palliative care patients (with or without a prior history of substance abuse) represents a serious and complex clinical occurrence. Perhaps the more difficult situations involve the patient who is actively abusing illicit or prescription drugs or alcohol concomitantly with medical therapies. Whether the patient is an active drug abuser, has a history of substance abuse, or is not complying with the therapeutic regimen, the clinicians should establish structure, control, and monitoring so that they can prescribe freely and without prejudice.

Multidisciplinary Approach

A multidisciplinary team approach is usually optimal for the management of substance abusers in the palliative care setting. If available, mental health professionals with specialization in addictions can be instrumental helping palliative care team members develop strategies for management and patient treatment compliance. Providing care to these patients can lead to feelings of anger and frustration among staff. Such feelings can unintentionally compromise pain management and contribute to feelings of isolation and alienation by the patient. A structured multidisciplinary approach can be effective in helping the staff better understand the patient's needs and develop effective strategies for controlling pain and aberrant drug use simultaneously. Staff meetings can be helpful in establishing treatment goals, facilitating compliance, and coordinating the multidisciplinary team.

Assessment

The first member of the medical team (frequently a nurse) to suspect problematic drug taking or a history of drug abuse should alert the patient's palliative care team, thus beginning the multidisciplinary assessment and management process (63). A physician should assess the potential of withdrawal or other pressing concerns and begin involving other staff (e.g., social work or psychiatry) to begin planning management strategies. Obtaining as detailed as possible a history of duration, frequency, and desired effect of drug use is crucial. Frequently, clinicians avoid asking patients about substance abuse because of fear that they will anger the patient or that they are incorrect in their suspicion of abuse. This stance can contribute to continued problems. Empathic and truthful communication is always the best approach.

The use of a careful, graduated interview approach can be instrumental in slowly introducing the assessment of drug use. This approach entails starting the assessment interview with broad questions about the role of drugs (e.g., nicotine, caffeine) in the patient's life and gradually becoming more specific in focus to include illicit drugs. Such an approach is helpful in reducing denial and resistance.

This interviewing style also may assist in the detection of coexisting psychiatric disorders. Comorbid psychiatric disorders can significantly contribute to aberrant drug taking behavior. Studies suggest that 37–62% of alcoholics have one or more coexisting psychiatric disorders and that drug history may be a clue to comorbid psychiatric disorders (e.g., drinking to quell panic symptoms). Anxiety, personality disorders, and mood disorders are the most common encountered (3,64). The assessment and treatment of comorbid psychiatric disorders can greatly enhance management strategies and reduce the risk of relapse.

Development of a Treatment Plan—General Considerations

Clinicians must control and monitor drug use in all patients, a daunting task in some active abusers. In some cases, a major issue is compliance with treatments for the underlying disease, which may be so poor that the substance abuse actually shortens life expectancy by preventing the effective administration of primary therapy. Prognosis may also be altered by the use of drugs in a manner that negatively interacts with therapy or predisposes to other serious morbidity. The goals of care can be very difficult to define when poor compliance and risky behavior appears to contradict a reported desire for disease-modifying therapies.

Clear treatment goals are essential in managing aberrant drug-related behaviors. Depending on the history, a complete remission of the patient's substance use problems may not be a reasonable goal. The distress of coping with a lifethreatening illness and the availability of prescription drugs for symptom control can undermine the effort to achieve abstinence (65). For some patients, “harm reduction” may be a better model. It aims to enhance social support, maximize treatment compliance, and contain harm done through episodic relapse (Table 41-5).

Involve a multicisciplinary team
Set realistic goals for therapy
Evaluate and treat comorbid psychiatric disorders
Prevent or minimize withdrawal symptoms
Consider tolerance when prescribing medications for pain and symptom control
Apply accepted guidelines for opioid therapy*
Accept patients' self-report of distress
Frequently reassess the adequacy of pain and symptom control
Recognize specific drug abuse behaviors
Use nonopioids and psychological techniques as indicated, but not as substitutes

*Recently published guidelines for long-term opioid pharmacotherapy are available.

TABLE 41-5. GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH SUBSTANCE ABUSE DISORDERS

To establish goals, the clinician should first establish a relationship based on empathic listening and accept the patient's report of distress. Second, it is important to

use nonopioid and behavioral interventions when possible, but not as substitutes for appropriate pharmacological management. Third, the team should consider tolerance, route of administration, and duration of action when prescribing medications for pain and symptom management. Preexisting tolerance should be taken into account for patients who are actively abusing drugs or are being maintained on methadone hydrochloride. Failure to address tolerance through proper dose selection and titration can result in undermedication and contribute to the patient's attempts to self-medicate. The use of medications with slow onset and longer duration (e.g., fentanyl transdermal and sustained-release opioids) may help to reduce the risk of aberrant behaviors in those with addictive disorders. Patients who are perceived to be at high risk should not be given short-acting opioids for breakthrough pain. Finally, the team should make plans to frequently reassess the adequacy of pain and symptom control.

Urine Toxicology Screening

Urine toxicology screening has the potential to be a very useful tool to the practicing clinician, both for diagnosing potential abuse problems and for monitoring patients with an established history of abuse. However, recent work suggests that urine toxicology screens are employed infrequently in tertiary care centers (66). In addition, when they are ordered, documentation tends to be inconsistent regarding the reasons for ordering as well as any follow-up recommendations based on the results. Indeed, the survey found that nearly 40% of the charts surveyed listed no reason for obtaining the urine toxicology screen and the ordering physician could not be identified nearly 30% of the time. Staff education efforts can help to address this and may ultimately make urine toxicology screens a vital part of treating pain in oncology patients.

Patients with Advanced Disease

Managing addiction problems in patients with advanced medical illness is labor and time intensive. This begs the question as to why a clinician should even bother to address such a complex health concern in the patient with advanced disease. In fact, many clinicians might opt to overlook a patient's use of illicit substances or alcohol entirely, viewing these behaviors as a last source of pleasure for the patient. However, addiction has a deleterious impact on palliative care efforts. Proper addiction management plays an important part in the success of palliative efforts to reduce suffering. Addiction behaviors may result in increased stress for family members, family concern over the misuse of medication, a potential for masking symptoms important for the patient's care, poor compliance with the treatment regimen, and diminished quality of life. Complete abstinence may not be a realistic outcome, but reduction in use can certainly have positive effects for the patient and family (67).

Outpatient Management

There are a number of strategies for promoting treatment adherence in an outpatient setting. (Table 41-6 outlines management strategies for outpatients who require palliative care and are actively abusing drugs.) A written contract between the care team and patient helps to provide structure to the treatment plan, establishes clear expectations of the roles played by both parties, and outlines the consequences of aberrant drug taking. The inclusion of spot urine toxicology screens in the contract can be useful in maximizing treatment compliance. Expectations regarding attendance at clinic visits and the management of one's supply of medications should also be stated. For example, the clinician may wish to limit the amount of drug dispensed per prescription and make refills contingent on clinic attendance. The clinician should consider requiring the patient to attend 12-step programs, and have the patient document his or her attendance as a condition for ongoing prescribing. With the patient's consent, the clinician may wish to contact the patient's sponsor and make him or her aware that the patient is being treated for chronic illness that requires medications (e.g., opioids, etc.). This action reduces the potential for stigmatization of the patient as being noncompliant with the ideals of the 12-step program. Finally, the team should involve family members and friends in the treatment to help bolster social support and functioning. Becoming familiar with the family may help the team to identify family members who are themselves drug abusers and who may potentially divert the patient's medications. Mental health professionals can help family members with referrals to drug treatment and codependency groups, as a way to help the patient receive optimal medical care.

Use written contracts
Use frequent clinic visits
Give small quantities of medications per prescription
Renew prescriptions contingent on clinic attendance
Use 12-step programs where possible
Use spot urine toxicology screens
Involve family in treatment planning

TABLE 41-6. MANAGEMENT STRATEGIES FOR OUTPATIENTS WHO REQUIRE PALLIATIVE CARE AND ARE ACTIVELY ABUSING DRUGS

Inpatient Management

The management of patients with active substance abuse problems who have been admitted to the hospital for treatment of a life-threatening illness both includes and expands on the guidelines discussed for outpatient settings. These guidelines aim to promote the safety of patient and staff, contain manipulative behaviors by patients, enhance the use of medication appropriately used for pain and symptom management, and communicate an understanding of pain and substance abuse management. The first point of order is to discuss the patient's drug use in an open manner. In addition, it is necessary to reassure the patient that steps will be taken to avoid adverse events such as drug withdrawal. For certain specific situations, such as for preoperative patients, patients should be admitted several days in advance for stabilization of the drug regimen. Also, it is important to provide the patient with a private room near the nurses' station to aid in monitoring and to discourage attempts to leave the hospital for the purchase of illicit drugs. Further, the team should require visitors to check in with nursing staff before visitation. In some cases it may be necessary to search the packages of visitors to stem the patient's access to drugs. As a final point, the team should collect daily urine specimens for random toxicology analysis and frequently reassess pain and symptom management (Table 41-7).

Have regular contact with floor staff and facility administrators to apprise them of necessary strategies
Document strategies in the medical record and note justification
Obtain private room close to nursing station
Search possessions and packages brought by visitors
Restrict patient's mobility (to room, floor, etc.)
Collect urine for toxicology screens daily

TABLE 41-7. MANAGEMENT STRATEGIES FOR INPATIENTS WHO REQUIRE PALLIATIVE CARE AND ARE ACTIVELY ABUSING DRUGS AT THE TIME OF ADMISSION

As with pain regimens, management approaches should be tailored to reflect the clinician's assessment of the severity of drug abuse. Open and honest communication between the clinician and patient reassures the patient that these guidelines were established in their best interests. In some cases, these guidelines may fail to curtail aberrant drug use despite repeated interventions by staff. At that point, the patient should be considered for discharge; however, our experience suggests that this is only necessary in the most recalcitrant of cases. The clinician should involve members of the staff and administration for discussion about the ethical and legal implications of such a decision.

Methadone Hydrochloride

Oral methadone hydrochloride can be used safely and effectively as an analgesic (68,69,70 and 71). The use of this drug has been increasing in recent years. Once-daily methadone hydrochloride is rarely useful as an analgesic and patients receiving maintenance methadone hydrochloride for opioid addiction cannot achieve pain relief merely by increasing the dose. Indeed, practitioners sometimes assume that patients receiving methadone hydrochloride from a maintenance program do not need further pain medication, but this is simply not true (72,73). Methadone hydrochloride can be used for pain management by increasing the dose and dividing it during the day. Alternately, an entirely separate pharmacological therapy can be chosen and incorporated into the patient's treatment plan.

Patients in Recovery

Pain management for patients in recovery presents a unique challenge. Depending on the structure of the recovery program (e.g., Alcoholics Anonymous, methadone hydrochloride maintenance programs), a patient may fear ostracism from the program's members or may have an increased fear regarding susceptibility to readdiction. The first choice should be to explore nonopioid therapies with these patients, which may require referral to a pain center (72). Alternative therapies may include the use of nonopioid or adjuvant analgesics, cognitive therapies, electrical stimulation, neural blockades, or acupuncture. If the pain condition is so severe that opioids are required, certain measures should be considered based on the outcome of a thorough assessment, reviewing the goals of care, informed consent, and the life expectancy of the patient. In some cases, then, it is necessary to structure opioid use with opioid management contracts, random urine toxicology screens, and occasional pill counts. If possible, an attempt should be made to include the patient's recovery program sponsor in the treatment planning process to garner their cooperation and aid in successful monitoring.

CONCLUSION

Although the most prudent actions on the part of clinicians cannot obviate the risk of all aberrant drug-related behavior, clinicians must recognize that virtually any drug that acts on the central nervous system, by any route of drug administration, can be abused. The problem does not lie in the drugs themselves. The effective management of patients with pain who engage in aberrant drug-related behavior necessitates a comprehensive approach that recognizes the biological, chemical, social, and psychiatric aspects of substance abuse and addiction, and provides practical means to manage risk, treat pain effectively, and assure patient safety.

An accepted nomenclature for abuse and addiction and an operational approach to the assessment of patients with medical illness are prerequisite to an accurate definition of risk in populations with and without histories of substance abuse. Unfortunately, there are very limited data relevant to risk assessment in the medically ill. Most data relate to the risk of serious abuse or addiction during long-term opioid treatment of chronic pain in patients with no history of substance abuse. There is almost no information about the risk of less serious aberrant drug-related behaviors, the risk of these outcomes in populations that do have a history of abuse, or the risk associated with the use of potentially abusable drugs other than opioids.

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42

PROGNOSTICATION IN ADVANCED DISEASE

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One meaning of *prognosis* is that it is a physician's estimate of the future course of a patient's disease and especially of their survival. Prognoses are important to physicians and patients in all phases of cancer care, and they inform both medical and nonmedical decisions. In early-stage disease, prognoses help physicians and patients to weigh the likely benefit of given therapies (e.g., adjuvant chemotherapy). In advanced stage disease, prognoses may be of additional importance, as they may herald a switch from primarily curative or life-prolonging care to primarily palliative care and in so doing set off a cascade of both clinical and personal decisions. Despite its importance and ubiquity, reliable prognostication in advanced disease is not straightforward. Numerous studies have revealed substantial optimistic bias in physicians' prognoses for their terminally ill cancer patients. It seems likely that this optimistic bias may contribute to the short survivals observed in patients referred for hospice care and to other types of decisions doctors and patients make near the end of life. Research that is focused on improving physicians' prognostic abilities is therefore of critical importance to palliative care.

PROGNOSTIC INACCURACY

Although prognosis is a central element of a significant amount of oncologic research, formal and explicit prognostication is not often required in the clinical care of cancer patients. Nevertheless, there are two instances in the care of advanced cancer patients where physicians are asked explicitly to prognosticate: (a) when they are enrolling patients on experimental chemotherapy protocols, and (b) when they are referring patients for hospice care. Each therapy has discrete and opposite eligibility requirements pertaining to survival— that is, to be considered for enrollment on phase I experimental chemotherapy protocols, patients typically must have an estimated survival of longer than 3 months. To be considered for enrollment for hospice care under the Medicare Hospice Benefit, patients must have an estimated survival of less than 6 months. Because of these formal requirements, physicians' ability to determine fine gradations in survival among patients in their last 6 months of life may mean the difference between aggressive and palliative care.

Optimism in Formulating Prognoses

How good are physicians at determining which patients are in their last 6 months of life? The answer may be found in literature pertaining to aggressive and palliative therapies for advanced cancer patients. From the experimental chemotherapy literature, Janisch and colleagues analyzed survival data from 349 advanced cancer patients after enrollment in phase I therapies (1). Overall, they found that the median survival was 6.5 months, well above the requisite 3 months described in most eligibility requirements. However, 25% died within 3 months (i.e., inconsistent with the prognostic standard), although very few of those with a performance status of more than 70 died before 3 months. Given the low clinical response rates associated with phase I therapies, it is unlikely that survival was enhanced by the therapies themselves. Therefore, results from this study suggest that physicians enrolling patients on phase I protocols are generally able to predict which patients have longer than 3 months to live. An alternate explanation is that other eligibility requirements, like performance status and laboratory tests, select for patients with longer than 3 months to live, obviating the utility of the physicians' prognostic assessment. Because the study was not designed to test physician prognostic accuracy, it is difficult to draw strong conclusions about the actual role of physician prognostication.

Within the palliative oncology literature, there are several studies specifically designed to determine physicians' prognostic accuracy in predicting survival of patients admitted to hospice programs (2,3,4,5,6 and 7). Investigators in these studies have measured physicians' prognostic accuracy by comparing patients' observed survival to their predicted survival (these predictions are not necessarily ones communicated to patients; rather, they are ones physicians formulate for themselves). Results of the studies, summarized in Table 42-1, show that, in aggregate, physicians' overall survival estimates tended to be incorrect by a factor of approximately three, always in the optimistic direction (2,3,4,5,6 and 7).

Primary investigator	Reference	Year	Number of doctors	Number of patients	Median estimated survival (wk)	Median actual survival (wk)	Estimated survival/actual survival
Parkes	2	1972	NR	103	4.9	2.9	1.8
Evans	3	1985	3	42	NR	NR	12
Heyse-Moore	4	1987	NR	53	8	2	4
Forster	5	1988	3	103	7	3.5	2
Maltoni	6	1994	4	100	6	5	12
Christakis	7	2000	343	468	NR	3.4	1.9

NR, not reported.
[a]Values estimated from graph in paper.
[b]Seven weeks calculated through statement in paper that survival was overestimated by 3-4 weeks on average.
[c]Ratio of mean estimated survival/mean survival.

TABLE 42-1. SUMMARY OF STUDIES COMPARING PHYSICIANS' ESTIMATED SURVIVAL TO PATIENTS' ACTUAL SURVIVAL

Studies of physicians' abilities to predict terminally ill cancer patients' survival are not limited to patients in palliative care settings but have also been evaluated in ambulatory patients undergoing anticancer therapy. Mackillop and Quirt measured oncologists' prognostic accuracy in the care of their ambulatory cancer patients by asking them to first predict patients' likelihood of cure and then to estimate the duration of survival for those whose likelihood of cure was zero (8). At the 5-year point, patients who were alive and disease-free were termed “cured”; the dates of death of the incurable patients also were determined. The researchers reported that oncologists were highly accurate in predicting cure. That is, for subgroups of patients (not individual patients) the ratio of the observed cure rate at 5 years to the predicted cure rate was quite high, at 0.92. However, the same oncologists had difficulty predicting the length of survival of individual incurable patients. They predicted survival “correctly” for only one-third of patients, with the errors divided almost equally between optimistic and pessimistic.

Optimism in Communicating Prognoses

Once a prognosis has been formulated, a physician must decide how to communicate it. This is the distinction between foreseeing and foretelling the patient's future (9). Although, as noted above, there is unconscious optimism in the prognoses physicians formulate regarding their advanced cancer patients' survival, there is also additional—and conscious—optimism in the prognoses physicians subsequently communicate to their patients. For example, one study asked physicians referring terminally ill cancer patients for hospice care how long they thought the patient had to live and also what prognosis, if any, they would provide to their patient if the patient inquired (10). It found that the median survival the physicians would communicate to patients was 90 days, their median formulated survival was 75 days, and the median observed survival was 24 days. This study revealed that the prognoses patients hear from their physicians may be more optimistic than what their physicians actually believe, which again is more optimistic than what actually occurs. Figure 42-1 shows the relationship between these three types of prognoses

(communicated, formulated, and observed).

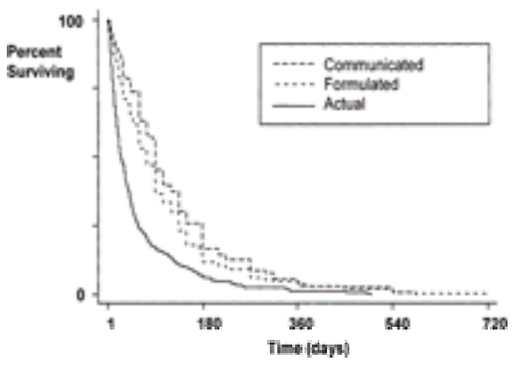

FIGURE 42-1. Relationship between physicians' communicated and formulated prognoses and their advanced cancer patients' actual survival after referral to hospice palliative care. [From Lamont EB, Christakis NA. Prognostic disclosure to patients with cancer near the end of life. Ann Intern Med 2001;134(12):1096–1105, with permission.]

In sum, although physicians are asked to foresee gradations of survival in advanced cancer patients enrolling in certain therapies (either aggressive or palliative), they are able to do so accurately less than a third of the time and, when in error, they generally tend to overestimate survival. This overestimation in formulated survival is compounded by an overestimation of communicated survival. Therefore, through their physicians' step-wise prognostic errors, advanced-stage cancer patients may become twice removed from the reality of their survival, both times toward a falsely optimistic prognosis.

PROGNOSTIC ACCURACY

Within palliative oncology, there is a growing literature focused on identifying predictors of survival of advanced cancer patients that might aid physicians in their prognostic estimates for similar patients. This literature is motivated not only by the centrality of prognosis to the care of such patients but also by physicians' inability to prognosticate accurately and their discomfort in doing so. Multiple prospective and retrospective cohort studies have consistently identified three broad classes of survival predictors: patients' performance status, patients' clinical signs and symptoms, and physicians' clinical predictions. New research seeks to increase the predictive yield of these clinical factors through models of increasing complexity that integrate these elements with each other and with new elements into easy-to-use composite measures. Additional new research in the broader oncologic arena of translational research seeks to exploit survival aspects of new biological markers [i.e., molecular (e.g., p53 [11], Her-2/neu [12])], although the extent to which these will aid in clinical prognostication in advanced disease is not yet established.

Performance Status

A performance status is a global measure of a patient's functional capacity. Because it has been consistently found to predict survival in cancer patients (13), it is frequently used as a selection criteria for patients entering clinical trials and also as an adjustment factor in the subsequent analyses of treatment effect. Several different metrics have been developed to quantify performance status, and among them, the Karnofsky performance status (KPS) is the most often used. The KPS ranges from values of 100, signifying normal functional status with no complaints nor evidence of disease, to zero, signifying death. The complete spectrum of values for the KPS scale is reproduced in Table 42-2.

Value	Level of functional capacity
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization is indicated although death is not imminent
20	Hospitalization is necessary, very sick, active supportive treatment necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

TABLE 42-2. KARNOFSKY PERFORMANCE STATUS SCALE

Multiple studies (1,3,6,14,15,16,17,18,19,20,21,22,23,24,25,26 and 27) have reported associations between cancer patients' survival and their performance status. The direction of the association is positive— that is, as a patient's performance status declines, so, too, does their survival. The magnitude of the association is described differently in different studies depending on the statistical methods used, but several studies report that among patients enrolled in palliative care programs, a KPS of less than 50% suggests a life expectancy of fewer than 8 weeks (3,6,14,16,27,28). The association between KPS value and survival in advanced cancer patients enrolled in palliative care programs is described in Table 42-3.

Index	Value	Median survival (d)	References
Karnofsky performance status	10–20	7–16	3,6,14,16,27,28,
	30–40	8–50	35
	≥50	50–90	
Anorexia	Present	≤58	14,28,35
Confusion	Present	≤38	28,35
Dysphagia	Present	<30	14
Dyspnea	Present	<30	14
Xerostomia	Present	<50	35
Leukocytosis	>8500 cells/μl	≤30	37
Doctor estimate	3 mo	30	2,4,7

TABLE 42-3. PREDICTORS OF SURVIVAL WITH ADVANCED CANCER UNDER PALLIATIVE CARE

Patients' Signs and Symptoms

Patients' clinical signs and symptoms have also been studied with respect to survival in advanced cancer. The usefulness of such indicators, even in preference to biological details of a patient's condition, was first outlined in a classic paper by Alvan Feinstein in 1966 (29,30). Recently, Vigano and colleagues engaged this topic in their qualitative systematic review of prognostic factors in advanced cancer (31). In examining 136 different variables from 22 studies, they found that, after performance status, specific signs and symptoms were the next best predictors of patient survival. The presence of dyspnea, dysphagia, weight loss, xerostomia, anorexia, and cognitive impairment had the most compelling evidence for independent association with patient survival in these studies. Table 42-3 contains the range of median survivals for the various symptoms reported in univariate analyses from these and other studies.

For example, numerous investigators have documented that dyspnea is inversely associated with survival in this patient population (14,16,26,33). The presence of dyspnea is associated with a survival of fewer than 30 days according to work by Maltoni et al. (14). Other investigators have described dyspnea as doubling the hazard of death (32). Similarly, others have shown inverse associations between dysphagia and survival (14,16,33,34), with Maltoni et al. describing an associated median survival of fewer than 30 days (14). Anorexia, confusion, and xerostomia are also inversely associated with survival (14,28,35), with median survival times of fewer than 60 days. These findings suggest that for advanced cancer patients such as those referred to palliative care programs, the presence or absence of these symptoms may help physicians to estimate patient survival.

Several groups of investigators have evaluated associations between biological markers (i.e., laboratory values) and survival in advanced cancer patients. For example, in their retrospective analysis of 339 phase I chemotherapy patients with advanced cancer at the University of Chicago, Janisch and colleagues found that among routine pretreatment laboratories, only platelet count elevation and serum albumin depression were associated with shorter survivals in a multivariate model that included KPS (1). Among a sample of 207 consecutive advanced non–small cell lung patients, Muers and colleagues found that in addition to performance status and symptoms, lymphocyte count, albumin, sodium, and alkaline phosphatase were all predictive of survival (36). Similarly, Maltoni and colleagues examined 13 hematological and urinary parameters at baseline and every 28 days in a group of 530 patients in Italian palliative care centers (37). In a multivariate model that included performance status, the investigators describe high total white blood cell count, low lymphocyte percentage, and low pseudocholinesterase as associated with diminished survival. Their Kaplan-Meier curves suggest that patients with elevated white blood cell counts (>8500 cell/μl) had median survivals of 1 month or less. The Janisch, Meurs, and Maltoni results are consistent; Janisch et al. found a strong correlation between platelet count and absolute neutrophil count and therefore dropped absolute neutrophil count from the final model. There may be a similar degree of correlation between albumin and pseudocholinesterase, both serum proteins. From these studies one can conclude that there appear to be negative associations between survival and bone marrow parameters (e.g., platelets, white blood cells) as well as positive associations between survival and synthetic parameters (e.g., serum proteins) in this patient population.

Physicians' Clinical Predictions

As noted previously, numerous studies suggest that physicians' predictions regarding patients' survival in palliative care programs are frequently incorrect and that the direction of the error is almost always optimistic. However, the overly optimistic estimates *are* correlated with actual survival (6,7,38). That is, although physicians are not wellcalibrated with respect to survival (i.e., they are systematically optimistic), they nevertheless have discriminatory abilities (39). They are able to order patients in terms of how sick they are or how long they have to live. This fact suggests that physicians' clinical predictions may be a useful, but not exclusive, source of information regarding patient survival. Thus, integration of clinical predictions with other known prognostic factors may be beneficial in predicting patient survival. For example, Muers and colleagues found that the addition of physician clinical prediction to their previously mentioned prognostic model (that contained performance status, symptoms, and laboratory values) improved the model's predictive power (36). This suggests that physicians are able to measure and quantify factors relevant to survival that are unmeasured by the previously mentioned factors. Similarly, Knaus and colleagues, in their Study to Understand Prognoses and Preferences for Outcomes and Risks for Treatments patients, found that multivariate regression models that included physicians' prognostic estimates were more accurate than the models without the physician input (40). Hence, although it is true that statistical models can be more accurate than human intuition alone (36,40,41), it is also true that physicians provide valuable prognostic information that, thus far, has not been captured in the objective models. Such integrated models hold the greatest promise for improving physicians' predictive accuracy in advanced cancer patients. Maltoni et al. explicitly combined this information with other known predictors of patient survival in their predictive tool (42).

Integrated Models

Investigators have also sought to model patient survival by combining and interacting these previously identified clinical predictors. Bruera and colleagues described a parsimonious model that combined three independently predictive elements (dysphagia, weight loss, cognitive failure) (34). They reported that the presence of all three poor prognostic factors among advanced cancer patients admitted to palliative care predicted death within 4 weeks, with a sensitivity of 0.74 and a specificity of 0.71. In this study, this measure performed better than physicians' clinical estimates of survival.

Using data from the National Hospice Study, Reuben and colleagues evaluated the initial performance status and symptomatology of 1592 terminal cancer patients admitted to hospice care and found that interacting the two survival predictors led to better prognostic modeling (16). That is, the survival associated with a given performance status depended on the number and type of additional symptoms. For example, patients with an initial KPS of 50% or more and no symptoms had a median survival of 172 days. This survival decreased to 125 days when dyspnea was also present at the initial evaluation. The survival decreased to 67 days when dyspnea, dysphagia, weight loss, and xerostomia were all present at the initial evaluation.

The most recent generation of studies describe integrated models that combine these and other prognostic variables into a single prognostic score. For example, Morita and colleagues developed a regression model predicting survival from performance status and certain clinical signs and symptoms (33). Coefficients from the regression were then transformed into partial scores, and summing the values of each partial score led to a final score termed the *Palliative Prognostic Index* (PPI). After developing the PPI in a sample of 150 patients, the investigators then tested the approach on a second sample of 95 patients, finding that the PPI predicted 3-week survival with sensitivity of 83% and a specificity of 85% and 6-week survival with sensitivity of 79% and a specificity of 77%. Table 42-4 contains a description of the PPI scoring system and Table 42-5 a summary of predictive relevance of PPI scores. Several other groups have developed similar scoring systems that rely on integration of all or some of the previously described classes of prognostic indicators of patients with advanced cancer and under palliative care (25,35,42). Such scoring systems need to be sensitive to a variety of methodological concerns (30,39,43,44 and 45). Further research is needed to determine if these scoring systems are useful in the clinical care of cancer patients and if they are applicable to patients who are not yet enrolled in palliative care programs or who are dissimilar from such patients. With respect to the clinical usefulness of the scoring systems, treating physicians will need to determine if the tools' test characteristics (e.g., sensitivity and specificity) fall above certain minimum thresholds for use in clinical decisions. Because of the issue of “zero time” (30,46) (i.e., the analytical impact of the selection of the time at which measurement of survival begins), many of the algorithms that rely on KPS, symptoms, or laboratory values obtained *after* referral to hospice may not be applicable to advanced cancer patients *before* referral to hospice.

Prognostic domains	Partial score value
Performance status	
10–20	4.0
30–50	2.5
≥60	0
Clinical symptoms	
Oral intake	
Moderately reduced	1.0
Severely reduced	2.5
Normal	0
Edema	1.0
Dyspnea at rest	3.5
Delirium	4.0

The scores from each prognostic domain are added, and the sum total is associated with a likelihood of survival either <3 weeks or <6 weeks. From Morita T, Tsundoa J, Inoue S, et al. The Palliative Prognostic index: a scoring system for survival prediction of terminally ill cancer patients. Support Care Cancer 1999;7:128–133, with permission.

TABLE 42-4. DESCRIPTION OF THE COMPONENTS OF THE PALLIATIVE PROGNOSTIC INDEX: A SCORING SYSTEM FOR SURVIVAL PREDICTION OF TERMINALLY ILL CANCER PATIENTS

Palliative Prognostic Index score	Median survival (d)
0.0–2.0	90
2.1–4.0	61
>4.0	12

[a]Median survival value was estimated from survival curve in paper.
From Morita T, Tsundoa J, Inoue S, et al. The Palliative Prognostic Index: a scoring system for survival prediction of terminally ill cancer patients. Support Care Cancer 1999;7:128–133.

TABLE 42-5. MEDIAN SURVIVAL OF PATIENTS ACCORDING TO PALLIATIVE PROGNOSTIC INDEX SCORE[a]

Other Sources of Prognostic Information

Other sources of information regarding survival in advanced cancer are studies that include cancer patients who do not undergo anticancer therapy. Both natural history studies and randomized therapy trials that include a "best supportive care" arm describe patients who do not undergo anticancer therapy. Typically, natural history studies are single institution case series of untreated patients with mortality follow-up. For example, Kowalski and Carvalho described the survival pattern of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (47). The median survival they report is 4 months. Others have looked at this issue in breast cancer (58) and hepatocellular cancer (48). Survival information can also be found by examining the survival of patients on the "best supportive care" arms of randomized clinical trials [e.g., trials in advanced non–small cell lung cancer (49,50,51 and 52), hepatocellular cancer (53), 5-fluorouracil refractory stage IV colon cancer (54), stage IV pancreatic cancer (55), stage IV gastric cancer (56)]. Table 42-6 contains a description of results of some of these trials (47,48,49 and 50,52,55,56,57 and 58).

Tumor site	Histology	Dx stage	Median survival*	N*	Reference
Breast	NR	NR	2.3 yr	1022	58
Colon	Adenocarcinoma	IV	5 mo	12	57
Gastric	Adenocarcinoma	IV	5 mo	38	56
Head and neck	Squamous cell	1/3 recurrent	4 mo	808	47
Lung	Non-small cell	IIIb/IV	4.1 mo	98	52
			5.3 mo	57	49
			5.9 mo	150	50
Liver	Hepatocellular	NR	1 mo	127	48
Pancreas	Adenocarcinoma	NR	3 mo	39	55

Dx, diagnosis; NR, not reported.
*Values pertain to the subset of untreated patients.

TABLE 42-6. MEDIAN SURVIVALS FROM STUDIES THAT INCLUDE UNTREATED PATIENTS

Prognostic Consultations

Another way for physicians to improve the accuracy of their prognostic estimates is to elicit prognostic estimates from disinterested colleagues. Through informal, "curbside" consultations or through more formal avenues such as tumor boards, physicians may find colleagues helpful in determining patient prognoses. This recommendation stems in part from results of several studies revealing that survival predictions averaged across physicians are more accurate than a prediction from a single physician (59,60) and from results of studies that show that disinterested physicians may provide more accurate predictions (7) than physicians with an emotional or other stake in the outcome of a patient's care. This technique may improve predictive accuracy and minimize optimistic bias by enhancing the "signal-to-noise ratio" in predictions or by decreasing "ego bias."

CONCLUSION

Prognostication in advanced cancer is a difficult task that may become easier as physicians become more comfortable with the process and as researchers begin to develop better clinical prediction tools. Such efforts will help abate the pervasive and systematic optimism in both the formulated and communicated prognoses physicians develop near the end of life. Ultimately, such improvement might be evident through increasing survival times after referral to palliative care programs. As physicians' predictive accuracy improves, survival after referral to hospice may approach physicians' ideal of 3 months (61) rather than the current survival of 3 or 4 weeks (7,62). More broadly, however, such improvement may provide patients with a better understanding of their expected survival and thereby allow them to make informed medical and social choices regarding their treatment path at the end of life, whether curative or palliative (63,64).

ACKNOWLEDGMENT

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43

EPIDEMIOLOGY OF CANCER AT THE END OF LIFE

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Although many advances have occurred in the prevention and treatment of cancer, death from this condition remains a common occurrence. The end-of-life experience associated with cancer varies widely and may be influenced by the type and extent of the disease and by the palliative interventions provided. Physical and emotional symptoms become more common as cancer progresses, and although there is evidence suggesting that they are often underused, many effective palliative interventions do exist to address these symptoms. Knowledge of the epidemiology of cancer-related mortality, symptoms, and end-of-life concerns is essential for physicians who care for patients and patients' families as they experience the advanced phase of illness. Such knowledge is necessary for several reasons: to facilitate optimal delivery of care and symptom management; to contribute to an informed public discussion about end-of-life care for cancer patients; to promote development of research initiatives targeted toward improving quality of life in the latter stages of illness; and to develop standards, guidelines, and treatment strategies for end-of-life care.

Oncology texts typically discuss the epidemiology of cancer in terms of prevalence, incidence, and patterns of disease. Consequently, there is a wealth of epidemiological data pertaining to the demographics of the population dying from cancer, including information about causes and locations of death. Yet there is a paucity of data describing the signs and symptoms of cancer and other factors that contribute to the quality of life at this end of the continuum of care. Due to the lack of empirical data, anecdotal personal narratives, although sometimes perceptive, have frequently been given great credence (1,2,3 and 4). This chapter reflects an attempt to provide the reader with some insight into the experience of advanced cancer toward the end of life. The first section of the chapter reviews aspects of the epidemiology of cancer-related death, including causes, mortality shifts, rates, life expectancies, patterns of institutionalization of medical care, and interactions between cancer patients and the health system. The chapter's latter section reviews the known prevalence of symptoms in the setting of progressive cancer, the nature of the dying process, and some of the problems that have, to date, hindered the development of a good understanding of the epidemiology of the symptom experience in the setting of advanced disease.

When describing the cancer experience, it must be acknowledged that there is a wide variability in this experience between countries. The epidemiological data presented in the chapter address some of the known differences, although much of the available information presented here focuses on the experience of cancer patients in the United States and other developed countries.

Although cancer impacts more than just the physical and emotional domains, the social ramifications of the epidemiology of cancer are not reviewed in this chapter. This is not to imply that these aspects of the cancer experience (including the impact of cancer on families, the social consequences of living with advanced cancer, the care delivered by health systems, and the honoring of the preferences of cancer patients) are not important, but the task given to the authors of this chapter was to address the “physical” aspects of the advanced cancer experience. Many of the issues related to the “social” impact of cancer are addressed in other chapters within this text.

MORTALITY STATISTICS

Leading Causes of Death

Before considering the epidemiology of the symptoms of advanced cancer and the end-of-life experience, it is helpful to have an understanding of where cancer ranks in comparison to other leading causes of death as well as the epidemiology of advanced cancer itself. It is also important to recognize that specific issues, including lifestyle, genetics, and health care, impact the cancer experience from country to country. Disease patterns vary from country to country as does access to care and many other factors.

World Health Organization statistics estimate that 56 million deaths occurred worldwide in 1999, and that 12.6% of these were due to cancer; of note, 31.1% were due to infectious or parasitic disease and 36.7% were due to circulatory or chronic obstructive pulmonary disease (5). Presently, cancer is proportionately more common as a cause of death in developed countries than in developing countries. Patterns of disease, however, indicate that the majority of deaths worldwide occur in developing countries, and that most of these deaths are still due to communicable diseases (6). Demographic shifts indicate that developing countries will have an increasing number of deaths due to noncommunicable disease (including cancer). By 2020, it is expected that deaths due to communicable and noncommunicable diseases will be equal (6).

Cancer Mortality

Statistics related to causes of death within developed countries share common patterns. The statistics of developed countries generally parallel those of the United States. In the United States, cancer was the second of the three leading causes of death in 1998, responsible for 23.2% of deaths (7,8). Cardiovascular disease was the cause of death in 31% of deaths and cerebrovascular disease in 7% (7,8). Cancer accounted for 27% of deaths in the United States in 1998 in those younger than 65 years of age and 22% of those older than 65 years (8). During the same year, there were 1.26 million new cases of cancer (excluding basal and squamous cell skin cancer and *in situ* carcinomas, except urinary bladder) and 541,519 cancer deaths (Table 43-1) (8). From 1990 to 1995, the overall age-adjusted cancer mortality rate in the United States declined by approximately 3.1%, the first sustained decline in cancer mortality since record keeping began in the 1930s (Fig. 43-1) (9).

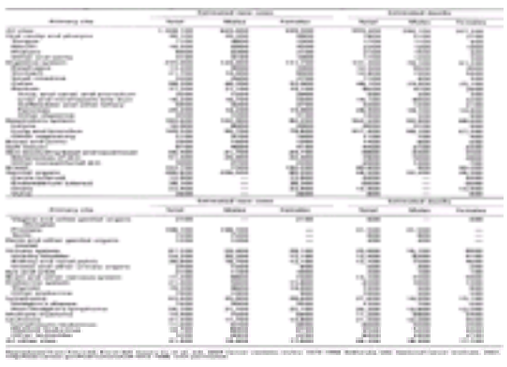

TABLE 43-1. ESTIMATED NEW CANCER CASES AND DEATHS FOR 2001 (ALL RACES, BY SEX)

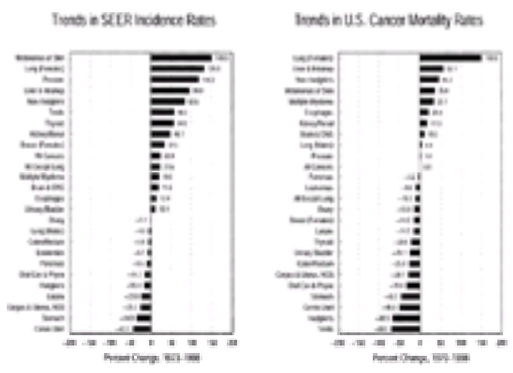

FIGURE 43-1. Trends in U. S. cancer incidence and mortality rates, 1973–1998. SEER, Surveillance, Epidemiology, and End Results. (From Ries LAG, Eisner MP, Kosary CL, et al., eds. SEER Cancer statistics review, 1973–1998. Bethesda, MD: National Cancer Institute, 2001 http://seer.cancer.gov/Publications/CSR 1973–1998, 2001, with permission.)

The estimated numbers for new cases of specific cancers and causes of cancer death in the United States are reported in Table 43-1 (8). Cancer of the lung is responsible for the largest number of deaths in the United States, with more than 154,000 deaths attributed to this condition in 1998, and almost 170,000 new cases estimated to be diagnosed (8). As is evident in Table 43-1, projected figures for 2001 indicate that little to no change is expected to occur, with 169,000 projected new lung cancer cases and 157,400 projected deaths (8). Data specific for each sex in the United States indicate that although the most common sites of new cancers in men are prostate (31%), lung and bronchus (14%), and colon and rectum (10%), the leading cause of cancer death in this population is cancer of the lung and bronchus (31%), with prostate next (11%), and colon and rectum accounting for 10% (10). In women, the most common sites of newly diagnosed cancer are breast (32%), lung and bronchus (13%), and colon and rectum (11%). Cancer of the lung and bronchus causes the greatest number of cancer deaths among women (25%), with breast cancer accounting for 15% and cancer of the colon and rectum responsible for 11% (10).

An important aspect of the epidemiology of cancer relates to the time period that individuals live with the condition. One way to understand this is to review the mortality and 5-year survival figures for different cancers. Many factors influence these figures, including age, sex, race, and treatment strategies. The 5-year survival rates for a variety of cancers from the United States cancer database are included in Table 43-2 (8). Time from diagnosis to death is another statistic used to document the duration of the illness experience. In the 1986 National Mortality Follow-back Survey, data on over 16,000 decedents in the United States were extrapolated to national mortality figures. The survey concluded that of the 511,114 cancer deaths during that year, 140,944 (27.5%) occurred within 6 months of the cancer diagnosis, 83,889 (16.4%) occurred 6–12 months after diagnosis, and 80,832 (15.8%) occurred 1–2 years later (11).

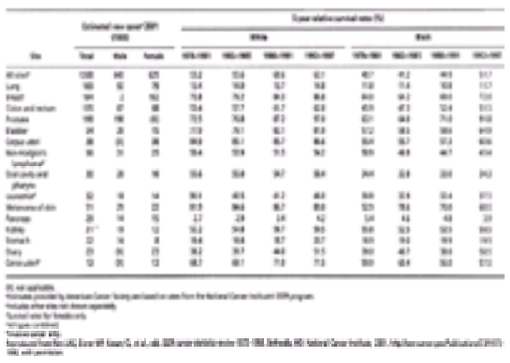

TABLE 43-2. CANCER— ESTIMATED NEW CASES, 2001, AND SURVIVAL RATES, 1978–1981 TO 1992–1997

Mortality Shifts

There are a variety of demographic factors that affect the patterns of disease and the management of any associated symptoms and distress. One of the most important factors is age. Causes of death, mortality rates, and trends in cancer death are different for different age groups. Cancer is most commonly a disease of the elderly, and therefore it is in this population that the symptoms of cancer most commonly require management. Age itself also affects mortality rates for specific illnesses. Mortality is higher as age increases (12). A worldwide shift toward an increase in life expectancy is therefore a key factor that will impact on demands on society to provide care for the elderly with cancer. The 1999 world population statistics report a total population of 6 billion, with a predicted increase to 8.9 billion by 2050. The average worldwide life expectancy has increased from 48 to 66 years in the past 50 years (6). In the United States, overall life expectancy has increased from 70.8 years in 1970 to 75.8 years in 1995 (13,14). With increasing life expectancies worldwide, and in spite of new cancer treatments and the declining incidence of certain cancers, it is presently expected that there will be a proportionate increase in cancer diagnoses and deaths from cancer (9,15,16,17,18,19,20 and 21).

Between 1994 and 1998, the median age at death for all cancers in the United States was 72 years, and for most cancers, the highest number of deaths occurs between 65 and 84 years (8). Although cancer is most common in the elderly, it is important to keep in mind that other age groups can be significantly impacted by cancer. For example, although malignant neoplasms were represented among the four major causes for death for every age group in the 2000 preliminary mortality figures for the United States, malignant neoplasms continue to be the *leading* cause of death in the 45–64 year age group (22).

In addition to age, many social and disease-related factors are likely to impact the ranking of the causes of death and the likelihood of death from cancer. There have been shifts in mortality rates, including an increase in lung cancer mortality rates, since 1973 (Fig. 43-1) (8). A major social factor affecting causes of death from cancer, and also from other causes, is smoking, which increases the prevalence of tobacco-related diseases. Other diseases, such as infection with the human immunodeficiency virus (HIV), can also increase the incidence of cancer in the population. In the United States, the HIV infection rate climbed an average of 16% annually from 1987–1995; however, since 1995 the HIV infection rate has been declining significantly, decreasing each year (by 28.8% from 1995 to 1996; by 47.7% from 1996 to 1997; by 20.6% from 1997 to 1998; and by 3.6% from 1998 to 1999) (22). Despite this decline, HIV disease continues to be the fifth leading cause of death among the 25–44-year age group (22). Worldwide HIV infection remains on the increase and significantly impacts mortality.

Interpretation of Mortality Data

When interpreting mortality data, it is important to note that most of this information is derived from death certificates. Death certificate data is often nonspecific and provides little detail that describes the end-of-life cancer experience. For example, “metastatic lung cancer” may be the identified cause of death, whereas respiratory or liver failure occurring as a consequence of metastatic lung cancer may have been the immediate cause of death. Although more detail would be helpful, it is seldom available. Autopsy data would provide more accurate information, but the rate of autopsies is low. For example, 268,553 autopsies were performed in the United States in 1993, representing only 9.7% of the deaths that occurred in that year (23). Autopsy rates were particularly low when death was attributed to one of the leading causes of death. For example, in 1993, the autopsy rate for death from malignant neoplasms was 2.5%. Less common causes of death, including those related to homicide, suicide, and accidents, were far more frequently investigated with autopsy. The autopsy rates in such cases were, respectively, 97.3%, 54.7%, and 48.4% (23).

Although premortem investigations in cancer patients often clarify the diagnosis and the extent of disease, the very low autopsy rate and the reliance on death certificate data for causes of cancer-related death significantly impact the evaluation of the dying process, both in individual cases and for the purpose of epidemiological research. Some of the information that is *not* available as a consequence of this problem includes data describing the specific “cause/s” of death for

many cancers. Although in individual cases the cause of death is often apparent to the clinician, statistical information is not available for many cancers to point to whether respiratory failure, liver failure, generalized cachexia, or other problems are the common contributory factors to death in specific types of cancer. This potential for inaccuracy, inherent in all data derived from death certificates, has important implications for the care of the dying. The lack of detailed, accurate information can impede the advancement in the medical understanding of the pathophysiology of symptoms and distress at the end of life. It may also contribute to delays in the development of symptom-specific palliative interventions (24).

Another important issue to consider when interpreting the data is that they do not reflect the burden of disease. A relatively new concept has evolved that could, over time, help to shed light on this issue worldwide—"disability adjusted life years." This concept attempts to quantify the burden of illness in relation to defined diseases by combining premature mortality and disability (25). Coupling this concept with statistics on causes of death may reveal information about the impact of cancer toward the end of life. World Health Organization indices suggest that the most burdensome medical conditions worldwide may be ischemic heart disease, stroke, and neuropsychiatric disease (25). Although there has been little information available about specific cancers and disability adjusted life years, more effort is currently being put into analysis of this concept so as to estimate the national burden of disease, in total and by disease entity. Brown et al. have published an excellent review of the indicators relating to burden of illness of cancer with respect to quality of life and economic cost (26). Within this publication, the authors report a personal communication from M. McKenna suggesting that the four most prevalent cancers (lung, breast, colorectal, and prostate) have the highest scores for disability-adjusted life years, with lung cancer far exceeding the others because its associated life expectancy is short and consequently large values of years of life are lost per individual (26). As information becomes available about this concept as it relates specifically to cancer, it may provide a helpful means of beginning to quantify the impact of cancer worldwide (26,27).

Place of Death

Although the demographics of cancer-related illness and death are useful in that they provide some understanding of the end-of-life experience, other information relating to cancer mortality is needed to provide an overall picture of the illness experience. The place in which death occurred provides some insights into this experience. In a survey undertaken in the United Kingdom of 98 cancer patients, of whom 84 (86%) agreed to be interviewed, 58% expressed a preference to die at home, 20% preferred the hospital, and 20% preferred an inpatient hospice (28). Sixty-seven percent of these patients, given improved health-related or social circumstances, indicated that they would prefer to die at home. Despite these preferences, most deaths in developed countries occur in medical institutions (29). High rates of institutional deaths are evident in Finland (75%), Sweden (79%), and Iceland (80%), whereas lower rates are recorded in some parts of Europe, in particular, Bulgaria (25%), Spain (30%), and Italy (37%) (29).

Death certificate data from the United States for 1990 indicate that of the 2.2 million annual deaths, approximately 62% occurred in hospitals, 16% occurred in nursing homes, and 17% occurred in homes (National Center for Health Statistics, *unpublished data*, general mortality, 1990, 1994). Home death was more common for patients with malignant neoplasms than for deaths from other causes, with 25.8% dying at home, 58.2% in hospitals, and 13.3% in nursing homes. These statistics also vary depending on age at which death occurs, the range being between 48% and 91%. For example, the place of death for individuals dying before the age of 14 years is highly likely to be a hospital (69–91%), whereas, at the other end of the age spectrum (those 85 and older), a high proportion of deaths (38%) occur in nursing homes.

Although hospital deaths are reported to be most common (National Center for Health Statistics, *unpublished data*, general mortality, 1990, 1994), this does not clarify the site of treatment during the weeks before death. A recent survey of the deaths of elderly individuals found that 45% spent the night before their deaths in a hospital and 25% were in a nursing home (30). Clinical experience suggests that moves between hospitals, homes, subacute care facilities, and hospices are not infrequent in the last weeks of life, but little research exists to specifically elaborate on this phenomenon in the cancer population.

Many social and disease-related factors also influence the place in which death occurs. For example, although hospice participation has been associated with a higher likelihood of death at home (31), the availability of hospice-associated inpatient beds increases the likelihood of death occurring in the inpatient setting (32). A cancer patient's symptom profile may also influence the site of death. For example, data from the 1981 National Hospice Study suggest that disorientation increases the likelihood that death will occur in the inpatient setting (32,33). The economics of health care delivery clearly influence national differences in sites of death and the site of death within a specific country. In developing countries in which access to health care may be limited, death is less likely to occur in an institution. In the United States, the increase in deaths at home or in hospices during the last two decades, which has been particularly evident in patients with cancer, may reflect changes driven in part by the development of a Medicare hospice benefit (34). The increase in the rate of nursing home deaths, particularly among the very elderly, may be related to changes in hospital reimbursement policies, such as prospective payment, utilization review, and preadmission screening (34,35). Some geographical trends also may relate, in part, to variations in the availability and reimbursability of hospice and home health care services. Differences may be compounded by variances in the availability of services in rural and urban areas.

Medical Involvement in Care Toward the End of Life

Those who die as a consequence of chronic illness in developed countries commonly have significant contact with health care professionals before death. The 1986 National Mortality Followback Survey reported that 81% of the 16,000 decedents studied received some institutional care during the last year of life, with 44% receiving between 1 week and 1 month of this care (11). Over 48% had seen a physician more than ten times during the last year of life. Almost 9% received hospice care at home, and less than 0.5% received inpatient hospice care. In a retrospective study of cancer deaths in the state of New York, investigators found that all of the patients surveyed had seen a doctor in the 6 months before death (36). Such contacts afford physicians many opportunities to play pivotal roles in the lives of those with advanced disease and their families by identifying specific needs and mobilizing resources to meet them.

Although physician contact with patients nearing the end of life may be common, the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT), although not specific to cancer patients, suggested that deficiencies were present in physicians' patient care roles at the end of life. For example, in the population in that study with colorectal cancer, physicians incorrectly identified patient preferences for cardiopulmonary resuscitation in 30% of cases (37). In addition, a lack of face-to-face contact between cancer patients and their physicians in the United States is evident as the time of death becomes very near (36). In the New York State survey of cancer deaths, 17% of patients had no contact with their physician, although more than half of these patients spent at least 1 of the last 2 weeks at home; 31% had only telephone contact during this period. The lack of face-to-face contact in the last 2 weeks of life is of concern because this is a time when symptoms are highly prevalent, and direct physician assessment and management of such concerns can be very important.

Systems of Care

An additional factor to consider when discussing care of the dying is the "system" of care in which medical care is provided. Access to health professionals with expertise in palliative or hospice care can be important toward the end of life. In some countries, "systems" specific to end-of-life care offer this type of access, whereas in others this type of care is incorporated into the system of care available through the entire course of illness. In the United States, *hospice* is defined broadly as a philosophy of care; however, from a practical perspective, it most commonly refers to a system of care distinct from the care system in the acute-care and hospital system. Toward the end of life, many cancer patients shift their care from an acute-care or hospital-based system to hospice care. Other patients who may have been cared for by a primary physician or a community-based oncologist may shift to hospice care but remain linked with their primary physician or oncologist for medical care. Patients who elect hospice do so, for the most part, at a time when they seek to focus on comfort and quality of life *without* pursuing life-prolonging interventions. Hospice offers an array of services delivered through a team approach, and aims to ensure quality of life for the patient and family, most commonly in the home setting.

In 1996, the National Hospice Organization estimated that 390,000 patients, or approximately 17% of deaths nationally, were treated in hospices in the United States (38). For 2000, the same organization reported that 600,000 individuals were receiving hospice care at the time of death, representing 25% of the deaths that occurred nationally (39). Of the deaths that occurred while patients were enrolled on hospice programs, 61% were reported to have occurred at home. The majority of hospice patients in the United States have a cancer diagnosis. It has been estimated that 58% of those in hospice care in the United States have a primary diagnosis of cancer and almost 40% of those who die of cancer receive hospice care (40). Despite this, and despite eligibility criteria that include those with a prognosis of less than 6 months' life expectancy, survival data suggest that patients spend only brief periods as hospice patients. There is a clear pattern of late referral to hospice. The National Hospice Organization reports a median hospice stay of only 25 days in the United States in 2000; 34% of deaths occurred within 7 days of admission (39). In a survey of 6451 hospice patients, 80.2% of whom had cancer, Christakis and Escarce found that the median survival after enrollment was 36 days, with 15.5% of the patients dying within 7 days (41). Survival was found to vary substantially according to cancer diagnosis even when adjustments were made for age and coexisting conditions. Table 43-3 contains the survival data for the cancer patients in this study. Of note, patients with breast, prostate, and central nervous system cancers had longer survival periods after enrollment than did patients with lymphoma, leukemia, or pancreas and colon cancer.

Diagnosis	Number of patients	Median survival (d)	Percentage who died within 7 d	Percentage who lived longer than 180 d
Leukemia or lymphoma	291	23.0	20.6	14.1
Urinary tract	256	34.0	14.1	12.9
Colon or rectum	678	24.5	15.8	12.4
Pancreas	289	21.0	18.3	10.0
Female genital tract	223	38.0	17.3	14.8
Upper gastrointestinal tract	221	28.0	13.1	9.0
Head or neck	101	44.0	17.8	13.9
Lung	1378	21.0	14.2	11.8
Breast	364	53.0	13.5	9.0
Central nervous system	141	46.0	7.1	14.2
Prostate	400	43.5	14.0	13.7
Liver or biliary tract	205	24.0	22.4	8.8
All other cancers	548	32.5	15.1	12.0

From Christakis NA, Escarce JJ. Survival of Medicare patients after enrollment in hospice programs. N Engl J Med 1996;335(3):172–178; with permission. Copyright 1988 Massachusetts Medical Society. All rights reserved.

TABLE 43-3. SURVIVAL ACCORDING TO CANCER DIAGNOSIS AMONG MEDICARE BENEFICIARIES ENROLLED IN HOSPICE PROGRAMS

Settings of Care and Quality of Care

Very little information exists about the variation in the quality of care delivered, or the “quality of life,” for patients in different settings. The 1981 National Hospice Study assessed 1754 terminal cancer patients in the United States and found that quality of life was similar for cancer patients in hospice and conventional care systems (42). Although some indicators in this study suggested that control of pain and other symptoms might have been better in the inpatient hospice setting (32,33), interpretation of the quality-of-life data in this survey is difficult owing to a variety of methodological problems. Although hospice programs generally offer an excellent spectrum of services and skills for patients with advanced disease, recent data are not available to compare the quality of life of hospice patients to that of hospital- or community-based patients who do not receive hospice care.

Other gaps in our understanding of quality of care and the quality of life near the time of death relate to information about care in subacute facilities and nursing homes, as well as in different parts of institutions, such as in intensive care units (ICUs) and oncology units. For example, in hospitals, even the *proportion* of intensive care–related deaths compared with ward deaths is unknown. Not only is quality-of-life data unavailable for patients in these settings, but there have also been little data thus far to quantify the proportion of patients who receive particular treatment interventions, such as palliative therapies, cardiopulmonary resuscitation, and mechanical ventilation.

An important study that has shed some light on the endof-life experience is the SUPPORT study, which investigated the experiences of 4301 seriously ill medical inpatients hospitalized in one of five teaching hospitals in the United States. This study found that a median of 8 days was spent in an ICU, in a coma, or with ventilator support, during the admission before death (43). The data from this study were combined with the information from another study of elderly patients to further explore the end-of-life experience associated with medical illness (37). The published data on lung or colon cancer patients in this population provide some particular insight into the cancer experience. For example, ICU admission was not as common for cancer patients as it was for other illnesses; only 3% of colon cancer patients underwent a resuscitation attempt; and only 2% received ventilator support.

Thus, in summary, the impact of the location or setting of care on quality of life during the dying process remains, to a large degree, unquantified. Although the proportion of patients dying in hospitals and at home varies with age, diagnosis, and numerous sociodemographical factors, the reasons for this variability and its implications for patient morbidity and quality of life are, to a very significant degree, still unknown.

“Trajectory of Illness”

Both performance status and level of consciousness contribute to the concept of a “trajectory of illness” or “trajectory of dying.” These are concepts that have been used to describe the similarities and differences in patient experiences over the course of illness and toward death (44,45,46,47 and 48). There is little information available to accurately describe the common trajectories for each particular cancer. The clinical perception of the experience for cancer patients, to date, reflects a combination of the trajectories B and C described in Figure 43-2 (48). Clearly the trajectory of illness is an individual experience, and is closely related to numerous other factors, including the disability that a particular cancer may cause, preexisting disabilities, the prognosis of that cancer, and the impact of treatment strategies focused on quality of life and maintenance of function. As treatments that are both symptom- and disease-specific evolve, it is feasible that the common trajectory of disease could begin to change. For example, it could reflect more of a combination of trajectories A and C.

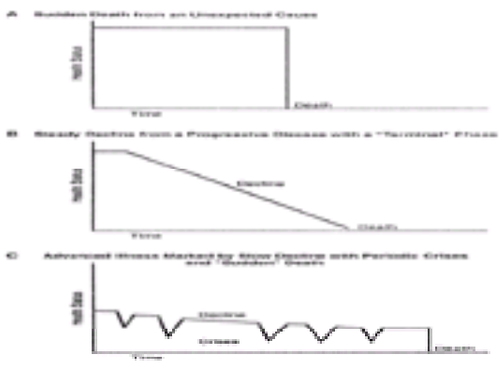

FIGURE 43-2. A–C: Death trajectories: This figure represents greatly simplified examples of three possible trajectories toward death. [Reprinted with permission from “*Approaching Death: Improving care at the end of life.*” Committee on Care at the End of Life; Field, M.J.; Cassel, C.K., Ed.; Institute of Medicine (U.S.). Copyright 1997 by the National Academy of Sciences. Courtesy of the National Academy Press, Washington, DC. (48).]

The trajectory of illness and death is an important consideration for a variety of reasons. First, because the preference of most individuals with cancer is to maintain function and quality of life for the maximum length of time, the trajectory of illness reflects in part whether this preference is being achieved. An understanding of the common trajectories is important to facilitate planning for expected contingencies. For example, if trajectory A were to reflect the more common course of disease progression, patients and families might need to be aware that precipitous functional decline and sudden death are possibilities. Trajectory B is likely to be associated with higher needs for physical assistance and support toward the end of life. Further, these issues are highly relevant when consideration is given to health system–related interventions for patients and their families. For example, the role and functioning of hospice programs would most likely need to be reconsidered if new treatments result in disease trajectories that differ significantly from those experienced now.

SYMPTOMS AND SIGNS OF ADVANCED CANCER (INCLUDING TOWARD THE END OF LIFE)

Despite growing interest in quality-of-life outcomes, oncological literature contains very little information about the nature of the advanced illness experience, the dying process, and the discomfort or distress associated with different cancers. Optimal health care planning, on an individual and a societal level, must anticipate potential problems to facilitate appropriate management. Without a clear understanding of the advanced illness experience and dying process, including recognition of common sources of distress for patients and families, the medical care of this population risks being suboptimal. Only a few studies undertaken in the hospice or palliative care setting have described the experience of the last months, days, or hours of life for patients with cancer. Until recently, there have been fewer data on hospitalized patients than on patients in palliative care and hospice settings, and this also represents a significant gap in knowledge. This section of the chapter reviews some of the data that exist to describe the “physical” experience of patients with cancer as they near the end of life.

Important Factors to Consider When Interpreting Surveys and Studies of Symptoms

At this juncture, before elaborating on the details of reports that address symptoms occurring toward the end of life, it is important to note that many of the existing surveys that attempt to specifically quantify symptom distress in cancer have a number of limitations. These limitations must be considered when interpreting all

surveys and studies of symptoms. It is hoped that investigators will begin to address some of these issues in future investigations.

A crucial issue to consider when interpreting symptom prevalence studies relates to study methodology. In interpreting reports of symptom-related distress, the subjectivity of reports must be considered. Symptoms are inherently subjective experiences, a factor that must be considered both at the bedside and when interpreting published reports of symptoms. *The Oxford Dictionary* has defined a symptom as “a physical or mental phenomena . . . specifically a *subjective* indicator perceptible to the patient and as opposed to an *objective* one (cf. sign)” (49). Symptoms must be distinguished from physical signs and observations that may not have been perceived by the patient as distressing. Proxy reports are common in the end-of-life setting, and although such reports can provide information that is obviously helpful—especially at times in illness when patients are unable to clearly communicate distress—they cannot provide subjective information. Although many patients have cognitive impairment near the very end of life (see the section Mental Status and Consciousness Before Death), the experiences in the last year of life in most patients with advanced cancer lend themselves well to surveys and studies that describe self-reported symptoms. Some use of proxy reporting to explore the important dimensions of distress in the very last week of life is necessary, but when such reports are used they must be interpreted with appropriate caution. There is a definite need for a common language and validated tools to begin to accurately quantify the experience of patients who are unable to communicate in this situation.

A second methodological issue relates to the fact that very few studies specifically explore the *dimensions* of symptoms. Symptoms are multidimensional, with dimensions including frequency, severity, and distress (50). In addition, there are associated correlates, including physical and psychological functioning. A simple report of the prevalence of a symptom does not provide information about the distress associated with the symptom, nor does it provide sufficient understanding of either symptom severity or impact (50,51 and 52). There is a paucity of data to clarify the impact of symptoms in the setting of far-advanced disease on function, physical or psychosocial needs, or the more global constructs of suffering and quality of life (53,54,55 and 56).

An example of the importance of the “dimensions” of symptoms is related to distress. Particularly at the end of life, the goals of the patient are likely to interface closely with distress. For example, a patient who is close to the end of life may consider comfort a higher priority than function and may reach a point where he/she does not consider impaired function distressing. Another patient, perhaps at an earlier stage of illness, may have great distress as a consequence of impaired function. Of note, in one survey of priorities toward the end of life of terminally ill patients in the United States, the majority highly prioritized freedom from pain and clarity of thought (57). Therefore, although reports of some symptoms (e.g., pain) are likely to correlate with at least some degree of distress, the mere presence of a symptom (e.g., fatigue) does not always correlate directly with distress.

Finally, with regard to data collection methodology in cancer patients, any report of global distress should be interpreted in the light of a high likelihood that more than one symptom is contributing to distress and impaired function. It is crucial that this variable be considered. For example, one study of cancer patients found that, although inpatients had more symptoms than outpatients, the mean number of symptoms per patient was 11.5 plus-or-minus 6.0 with a range of 0–25 symptoms (52).

Problems with study methodology are all related to the concept of “self-report” of symptoms. Given the prevalence of impaired consciousness as the very end of life approaches (see the section Mental Status and Consciousness Before Death), the exploration of some of these issues can be challenging in settings in which this problem is prevalent. It must be noted, however, that opportunities for further research abound in this population, as many patients do retain their ability to communicate until the very last days or hours of life (11,30,58,59 and 60).

Another problem in interpreting reports of symptoms and distress in cancer patients is that many investigations fail to describe in detail the medical and pharmacological interventions used for symptom management. This is one of the major problems encountered in the reporting of symptom distress toward the end of life. When such descriptions are absent, it cannot be ascertained if the high incidence of pain or any other reported symptom reflects a worsening pathological condition, undertreatment of the symptom (or symptom distress), or both. Nonetheless, it is known that the undertreatment of pain and other symptoms is likely to contribute to symptom distress, despite the existence of many effective treatment strategies. For example, it has been demonstrated that many cancer patients in the United States continue to receive inadequate analgesia (61,62). In a survey of 1308 oncology outpatients being treated by the physician members of the Eastern Cooperative Oncology Group, 67% reported recent pain and 36% described pain severe enough to impair function (61). This study also reported that over 40% of patients who reported pain did not receive adequate analgesia. Eighty-six percent of the physicians believed the majority of cancer patients with pain were undermedicated (62). Poor pain assessment was rated by 76% of physicians as the single most important barrier to adequate pain management, and 61% indicated that physicians' reluctance to prescribe opioids was another barrier. In a similar survey in France, 69% of cancer patients rated their worst pain at a level that impaired their ability to function, and undertreatment was again a prominent factor (63). As a consequence of these problems, it is difficult to ascertain the degree to which the distress reported in many surveys could have been alleviated. In summary, it is quite possible that much of the reported distress in existing surveys could have been alleviated with appropriate, state-of-the-art palliative interventions. Many such interventions are described in other chapters within this textbook.

In addition to considering “symptom-directed therapies” when interpreting reports of medical interventions and their impact on symptoms, one must also consider the potential impact of therapies directed toward the cancer itself. Many treatment strategies have evolved significantly over the years, and these changes impact both symptoms and the trajectory of the end-of-life experience for some cancers. The reports discussed below, some of which are now somewhat dated, may no longer reflect the current course of illness for some cancers.

Symptoms Present in the Setting of Advanced Cancer

Despite the gaps in treatment and knowledge and problems with the methodology of symptom assessment, a number of existing studies highlight the spectrum of symptoms experienced by cancer patients who live with advanced cancer and are nearing the end of life. These studies also provide some insights into the requirement for further studies to characterize the end-of-life experience and the dying process. The “end of life” can be defined in various ways; this review focuses on the symptoms present in the setting of advanced cancer and specifically discusses the last week and days of life in an attempt to illuminate, at least to some degree, the dying experience.

Many investigators have explored the spectrum of symptoms experienced by cancer patients at various points during the course of the disease. To explore the advanced illness experience, a number of studies have focused on the prevalence and impact of symptoms in the setting of advanced malignant disease (51,52,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80 and 81). Patients in the advanced stages of cancer commonly report fatigue, pain, anxiety, and anorexia, each with prevalence rates greater than 50% (51,52,77,78,81,82,83,84,85,86 and 87). Moreover, most patients with advanced cancer experience multiple symptoms (52,81,83,85). In an example of a study that used excellent methodology to assess an advanced cancer population, Portenoy et al. evaluated 243 cancer patients, almost two-thirds of who had metastatic disease. Over half were inpatients at the time of assessment (52). Across tumor types, 40–80% experienced lack of energy, pain, drowsiness, dry mouth, insomnia, or symptoms indicative of psychological distress. Although symptom characteristics were variable, the proportion of patients who described a symptom as relatively intense or frequent always exceeded the proportion describing it as highly distressing. In seeking to evaluate symptom distress, this study did not describe interventions for treatment of symptoms and their efficacy.

Studies of the experience of children with cancer are even less common than studies in the adult population. One study that highlights the spectrum of symptoms and the associated distress is from Collins et al., who studied 160 children with cancer between the ages of 10 and 18 years (45 inpatients, 115 outpatients) using a modified version of the Memorial Symptom Assessment Scale (88). Symptom prevalence ranged from 49.7% for lack of energy to 6.3% for problems with urination. The most common symptoms (those with a prevalence of greater than 35%) were lack of energy, pain, drowsiness, nausea, cough, lack of appetite, and psychological symptoms (feeling sad, feeling nervous, worrying, feeling irritable). Of the symptoms with prevalence rates greater than 35%, those that caused high distress in more than one-third of patients were feeling sad, pain, nausea, lack of appetite, and feeling irritable. The mean number of symptoms per inpatient was 12.7 (range, 4–26), which was significantly more than the mean number, 6.5 (range, 0–28), of symptoms per outpatient. Patients who had recently received chemotherapy had more symptoms than patients who had not, and patients with solid tumors had significantly more symptoms than patients with either leukemia, lymphoma, or central nervous system malignancies. As with the Portenoy et al. study, this study sought to evaluate symptom distress but did not describe interventions for the treatment of symptoms.

Among the physical symptoms experienced by patients with advanced cancer, pain and dyspnea are the two that have been most frequently, specifically surveyed. Large studies have documented that pain is experienced by 70–90% of patients with advanced cancer (89,90,91 and 92). In a survey conducted by Addington-Hall of 2074 patients who died from cancer in the United Kingdom, observers noted that 88% of patients had been in pain at some point during the last year of life, with 66% reporting to have found the pain “very distressing” (93). Other common symptoms reported in more than half of this population during the last year of life were loss of appetite, constipation, dry mouth or thirst, vomiting or nausea, breathlessness, low mood, and sleeplessness (93). Again, it must be noted that these studies do not address the degree to which symptom management strategies were implemented.

With regard to pain, some studies have specifically looked at the experience of patients at the very end of life. For example, the National Hospice Study (N = 1754), conducted in 1986 in the United States, indicated that pain became more prevalent in cancer patients during the last weeks of life (72). Although a large proportion of these patients were unable to be interviewed directly, 25% of those who could self-report indicated that persistent or severe pain was present within 2 days of death; this proportion was an increase from 17% in the previous 6 days. Another survey demonstrated that 80% of cancer outpatients experienced pain as death approached (67). A study focusing on the use of analgesics revealed that only 35% of patients dying in the home care setting and 9% in hospital-based hospice care did *not* use analgesics during the last week of life (75), but there may be serious limitations in the knowledge and skills of health professionals that have, to date, impacted the effective prescribing of these medications. A demonstration of this may be found in the SUPPORT study in the United States. In this large study of hospitalized patients, 50% of the 1400 patients who had been conscious before death were reported by caregivers to have experienced moderate to severe pain for at least half of

the time during their last 3 days of life (43). The data from this study were combined with data from another survey to clarify the perceptions of family members who observed the dying experiences of 3357 patients, of whom approximately 12% had lung cancer and 5% had colon cancer (58). In the groups with cancer, 40–46% of patients were judged by their relatives to have had moderate to severe pain for more than half of the time during the last 3 days of life.

To a lesser degree than pain, cancer-related dyspnea has also been explored. This symptom has been reported to be in the range of 20–78% in the advanced cancer setting (74,76,79,94). This wide variation likely reflects variability in the definition of dyspnea, in the methods used to elicit the symptom, and in methods of patient selection. These studies also involved patient populations with differing cancers, stages of illness, and treatment strategies. In many of these studies, distress was not clearly quantified, and, as is often the case with pain studies, details of symptom management strategies were not reported. Of note, it is also possible with this particular symptom that at least some of the observers in these studies may have provided reports of dyspnea when what was witnessed was actually the very common occurrence of heavy (and probably nondistressing) breathing at the end of life. These considerations must be taken into account for all of the studies on dyspnea discussed in this section. In the 1986 National Hospice Study, dyspnea was reported to have been seen in 70% of 1754 patients during the final 6 weeks of life, with the prevalence increasing as death approached (74). Higginson and McCarthy studied a group of 86 cancer patients and noted that dyspnea was a severe and often uncontrollable symptom near death (76). In a survey of hospice inpatients with cancer, dyspnea was present in 55.5% of all patients on admission to the inpatient hospice and 78.6% of those who died within 1 day of admission (79). In the SUPPORT study, dyspnea was reported to have been perceived by others to have been moderate to severe for the last few days of life for 30% of colon cancer patients and for almost 70% of those with lung cancer. Again, “perceived” distress with the observation of “heavy” breathing may be an issue in this report. There is a great need for focused studies that explore the prevalence, associated distress, and management of dyspnea.

Although the most common symptoms of advanced cancer are generally considered to be physical (e.g., pain, fatigue, or nausea), this finding can be ascribed to survey methodology that often does not address psychological symptoms. When specific psychological measures are incorporated into survey methodologies, high prevalence rates for psychological symptoms have been reported (65,68,70,80,95,96). For example, depressed mood and anxiety have been commonly reported in response to specific questions addressed to ambulatory cancer patients (52). Other chapters in this textbook provide more detail about the prevalence of, and treatment strategies for, psychological symptoms.

Impact of Symptoms in Advanced Cancer

As discussed, data that relate *only* to the prevalence of symptoms do not provide sufficient understanding of symptom severity, distress, or impact (50,51 and 52). Only a small amount of information is available to quantify the specific impact of symptoms in advanced disease on function, physical or psychosocial needs, or on the more global constructs of suffering and quality of life. The use of some of the newly developed instruments for assessment of these constructs may, over time, improve our understanding of these issues (50,97,98,99,100,101,102,103,104 and 105).

Chang et al. recently surveyed 240 patients with advanced cancer at a Veterans Affairs Hospital in the United States (81). This survey, using excellent symptom assessment methodology, provides some insights into the impact of increasing numbers of symptoms on the presence of other symptoms, performance status, and quality of life. The median number of symptoms was eight per patient (range, 0–30 symptoms), but those patients with “moderate intensity pain” had a median number of 11, and those with a “moderate-intensity lack of energy” reported a median of 13. The five most prevalent symptoms were lack of energy (62%), pain (59%), dry mouth (54%), shortness of breath (50%), and difficulty sleeping (45%). Patients with a level of pain or fatigue that was “moderate” were noted to have more symptoms than those with lesser intensity ratings for these symptoms. As was the case in the Portenoy study (52), referenced in the section Symptoms Present in the Setting of Advanced Cancer, the proportion of patients who described a symptom as relatively intense or frequent always exceeded the proportion describing it as highly distressing, although symptom characteristics were variable (Table 43-4). As the number of intense symptoms increased, performance scores decreased. In addition, the number and intensity of symptoms also correlated with quality-of-life scores, even when the symptom-specific items from the quality-of-life measures were removed (81).

Symptom	Prevalence (%)	Severe distress (%)
Lack of energy	62	60
Pain	59	52
Dry mouth	54	12
Shortness of breath	50	16
Difficulty sleeping	45	20
Feeling drowsy	44	16
Worrying	40	12
Feeling nervous	37	20
Cough	33	18
Weight loss	33	11
Lack of appetite	29	15
Feeling irritable	28	17
Sexual interest	18	7

Modified from Chang VT, Hwang SS, Feuerman M, et al. Symptom and quality of life survey of medical oncology patients at a Veterans Affairs medical center: a role for symptom assessment. Cancer 2000;88(5):1175–1183. Copyright 2000 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

TABLE 43-4. PREVALENCE OF SYMPTOMS AND SYMPTOM DISTRESS IN MEDICAL ONCOLOGY PATIENTS AT A VETERANS AFFAIRS MEDICAL CENTER (N = 240)

The National Mortality Followback Survey (see the section Cancer Mortality) also provides some insights into the impact of illness at the end of life. This was undertaken by the collection of information from death certificates and from the responses to a proxy survey questionnaire completed by the caregiver of each decedent (106). Although the most recent survey, conducted in 1993, evaluated over 18,000 decedents, specific information is not available about the 32% of individuals who had a history of cancer. Nonetheless, the reports of the functional impairment of the population as a whole during the last year of life revealed that 37% patients had some trouble with preparing meals, 54% with walking, and 34% with eating. Nearly half (42.1%) of patients spent 14 days or more (and 15% spent more than 6 months) of the last year of life in bed for more than half the day (106). The differential impact of symptoms on these limitations was, unfortunately, not quantified in the survey, but information about this, along with data specific to cancer, could provide insights into the end-of-life experience of cancer patients. In the survey by Addington-Hall (discussed in the section Symptoms Present in the Setting of Advanced Cancer) of 2074 cancer deaths in the United Kingdom, district nurse assistance was needed for at least 60% of the deceased, home help in 20%, and “meals on wheels” in 9% (although relatives bore the brunt of caring for 81%). In spite of this, 31% were reported to have needed “more help” with activities of daily living. It would seem that symptoms may have been limiting in these instances, but the exact relationship of symptoms to activities of daily living was not elaborated on (93).

Some investigators have attempted to correlate the presence of symptoms with prognosis (84,107,108). Such analyses are very complex, with conclusions that are likely to vary greatly in relation to different cancers, age groups, and other variables. The National Hospice Study in the United States (84) found that the Karnofsky Performance Status was the strongest predictor of survival in terminally ill patients. Within this study it was also reported that five symptoms—dry mouth, shortness of breath, problems eating, recent weight loss, and trouble swallowing—had some predictive value in relation to survival time. When low levels of performance were present, prognosis was poor regardless of which symptoms were present. In a recent large Italian study of cancer patients in a palliative care setting, Caraceni et al. found that the presence of delirium, along with some other factors (including low performance status), was predictive of shorter survival (108). Further studies are needed to accurately describe the impact on prognosis of symptoms and their treatment.

Symptom Distress in the Immediate Period before Death

A survey of 486 dying patients undertaken by Dr. William Osler between 1900 and 1904 represents the first important survey of the dying process. In this survey, a questionnaire was completed by the nurse who attended the patient at the hour of death (109,110). This survey was not confined to cancer patients. Osler described most patients as dying comfortably with “no sign of death one way or another . . . like their birth, death was a sleep and a forgetting.” Despite this, many patients experienced distressing symptoms at least transiently. The distress was described as “bodily pain or distress” (N = 90), “mental apprehension” (N = 11), “positive terror” (N = 2), and “bitter remorse” (N = 1). The study did not go on to describe the palliative interventions used to treat this distress, although it is known that Osler used opioid analgesia and held the view that uncontrolled symptoms should be adequately treated.

Subsequent to this survey, other investigators have explored aspects of the dying process, including mental status and consciousness before death, individual awareness of impending death, and the distress experienced by the dying. Many of these studies have focused on cancer patients, mainly in the United Kingdom, Europe, and Canada, with very few conducted in the United States. Some investigators have attempted to explore the time “near to death” by addressing symptoms thought to be markers of impending death at specific times, such as at admission to a hospice or a palliative care unit (82,83,96,111,112 and 113). Some studies have looked at care delivery near the end of life by attempting to examine the differences in the quality of care provided by inpatient hospice, palliative care, and home care services (33,87,114,115,116 and 117). Several investigations, including those summarized in Table 43-5, have used methodology that reflects an attempt to focus

specifically on the “dying process” or the last week of life (30,42,60,84,85 and 86,94,118,119,120,121,122,123,124,125 and 126).

Symptoms	Bedard (123) N = 152[a,b] (%)	Coyle (85) N = 90[a] (%)	Fainsinger (86) N = 100[a,b] (%)	Hinton (121) N = 82[a] (%)	Lichter (122) N = 220[a,b] (%)	Saunders (118) N = 200[a,b] (%)	Ward (102) N = 200[a,b] (%)
Pain	15–30	54	99	71	51	35	62
Dyspnea	9	28	46	4–28	22	21	52
Nausea	16	13	31	12–17	14	3	—
Vomiting	16	—	—	12–17	14	7	38
Sleepiness	5	57	—	—	—	46	—
Congestion	—	6	—	—	56	50	—
Confusion	4	28	35	—	9	52	39
Restlessness	—	7	—	—	42	31	—
Anorexia	14	6	—	—	—	—	61
Fatigue	—	52	—	—	—	—	—
Urinary incontinence	4	6	—	—	22	—	28

Symptoms were recorded if any two surveys demonstrated a prevalence of greater than 25% or if any one survey demonstrated a prevalence of 50% or more for a specific symptom.
[a]Hospice or palliative care inpatients only.
[b]Data provided by patient or primary caregiver.
[c]Cancer center inpatients and outpatients.
[d]Medications or overall distress included as one or as prevalence.
[e]General patients, type of care not specified.
[f]Data provided directly by patient.

TABLE 43-5. SYMPTOM PREVALENCE IN THE LAST WEEK OF LIFE IN PATIENTS WITH CANCER

Unfortunately, there are still large gaps in our knowledge, particularly regarding death from specific cancers in the hospital or home care setting. Data from hospice programs and numerous pain studies suggest that most deaths can be peaceful (86,118,123), although many studies suggest that at least transient distress is common and requires close attention and treatment. Among the large surveys, Osler's report suggested that approximately one-fifth of dying patients experienced some bodily pain or distress (109). This proportion is smaller than suggested in more recent surveys. For example, Brock et al. surveyed caregivers of elderly decedents in the United States, and although not all of these patients had cancer, it was reported that during the 24 hours before death, 44% of dying patients were short of breath, and 33% were in pain (30,60). The SUPPORT study reported that in the groups of patients with cancer, 40–46% were judged by their relatives to have moderate to severe pain for more than half of the time during the last 3 days of life (58). In addition, 30% of colon cancer patients and almost 70% of those with lung cancer were reported to have moderate to severe dyspnea for the last few days of life. Again, it is important to note the difficulty inherent in interpretation of this study, which used family observers to quantify distress. Nonetheless, the fact that this was the perception of families of patients at this time of life is very concerning, especially when it is known that a myriad of treatment strategies for these symptoms exist, and, as demonstrated by the hospice studies, death can usually be peaceful with close monitoring and treatment of distress.

Longitudinal studies can also provide insight into the patient experience in the setting of far advanced cancer at the end of life. Coyle et al. (85) reviewed the records of 90 cancer outpatients, ranging in age from 23 to 82 years, to describe their experiences during the 4 weeks before death. Two-thirds of these patients had cancers of the lung, colon, or breast, and all were cared for at home during this time. Only 19% of patients were able to engage in some form of limited activity outside the home. Fifty-seven percent died at home, 41% in the hospital, and 2% in an emergency room. At various times in the last 4 weeks of life, patients spontaneously identified 44 different symptoms distressing enough to interfere with activity. The number of symptoms volunteered per person ranged from one to nine, with 71% describing three or more distinct symptoms at 4 weeks before death. Fatigue (58%), pain (54%), weakness (43%), sleepiness (24%), and cognitive impairment (24%) were the most prevalent symptoms (Table 43-6). Although the spectrum of symptoms reported was similar at 4 weeks and 1 week before death, there were changes in prevalence. The prevalence of sleepiness increased from 24% to 57%, whereas the prevalence of pain decreased from 54% to 34%. Although the population depicted in this survey had been referred because of difficult pain problems, the degree of distress remains informative. Eighteen of these patients acknowledged suicidal ideation, and an additional four patients were suicidal, each elaborating a specific plan. The latter patients were clinically depressed and required psychiatric intervention. Four patients made a specific and spontaneous request for euthanasia without direct or indirect prompting from the clinician. Again, this survey highlights the common occurrence of symptoms and the importance of close medical and nursing monitoring of cancer patients near to the time of death to ensure that distress is alleviated promptly.

Symptom	4 weeks before death [N (%)]	1 week before death [N (%)]
Fatigue	52 (58)	47 (52)
Pain	49 (54)	31 (34)
Generalized weakness	39 (43)	44 (49)
Sleepiness	22 (24)	51 (57)
Mental haziness, confusion	22 (24)	25 (28)
Anxiety	19 (21)	16 (18)
Weakness of legs	16 (18)	15 (17)
Shortness of breath	15 (17)	25 (28)
Nausea	11 (12)	12 (13)
Decreased hearing	8 (9)	5 (6)
Depression	7 (8)	4 (4)
Loss of appetite	7 (8)	5 (6)
Inability to sleep	6 (7)	5 (6)
Weakness of upper limb	6 (7)	5 (6)
Cough	5 (6)	6 (7)
Restlessness/irritability	5 (6)	6 (7)
Swollen limb	4 (4)	7 (8)
Constipation	4 (4)	6 (7)
Difficulty swallowing	3 (3)	6 (7)
Pulmonary congestion	1 (1)	5 (6)
Dizziness	1 (1)	5 (6)
Incontinence	2 (2)	5 (6)
Difficulty speaking	5 (6)	5 (6)

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TABLE 43-6. PREVALENCE OF SYMPTOMS VOLUNTEERED BY ADVANCED CANCER PATIENTS 4 WEEKS AND 1 WEEK BEFORE DEATH (N = 90)

Impact of Medications on Symptom Management and Comfort at the End of Life

Specific strategies have evolved in the fields of pain management and palliative care to address common symptoms toward the end of life; these have been described in the literature and discussed at length in other chapters within this textbook. Effective treatment strategies exist for the most common symptoms, including pain, dyspnea, fatigue, confusion, and sleep disturbances. Clearly, however, there are some symptoms (e.g., fatigue) that may be somewhat difficult to resolve *completely* at the very end of life despite the existence of useful treatment strategies. Also, sedation occasionally may be a side effect encountered in the course of attempts to achieve symptom control at the very end of life. Accurate assessment of the impact of drugs used for symptom control, and assessment of the degree to which sedation is a necessary symptom management intervention, has been hampered by several problems. These include poor symptom assessment methodology and evidence that suggests many clinicians are still lacking the knowledge and skills needed to optimally implement known treatment strategies (61,62,127,128).

The debate regarding the role of sedative medications in the management of unendurable symptoms at the end of life highlights this dilemma. Ventafridda et al. triggered a controversy in the palliative care literature by reporting that 52.5% of dying patients required sedation to obtain relief from symptoms (124). This finding contrasted sharply with data from hospice programs, which suggest most deaths are peaceful (118,123). Ventafridda's results also differ from the results of a survey of 100 cancer patients in a palliative care setting in which the majority of deaths were comfortable, with only 18% of patients requiring sedating treatment for pain or delirium (86). In this latter study, 57% of patients were unresponsive by the day of death. Routine symptom assessment measures were used by Fainsinger et al. in this latter study, but interpretation of the data was difficult in both studies. First, symptoms were evaluated by observers, and second, no detailed descriptions of the palliative interventions were included. The proportion of patients who have intolerable symptoms, therefore, remains unresolved.

Further studies of treatment strategies, incorporating comprehensive symptom assessment measures, are needed to clarify the impact of therapy on symptom management for the dying. Research into these issues must be broadened to include individuals whose death occurs at home or outside of palliative care and hospice settings. Although the role of sedative drugs for management of refractory symptoms in the dying is controversial (86,124,126,129,130,131,132 and 133), the major concern for society continues to be the underuse of palliative strategies for the management of distress.

Mental Status and Consciousness before Death

A final aspect of the “physical” experience of advanced cancer relates to the ability to communicate toward the end of life. Although the prioritization of this by patients who have reached the last few days of life has not been explored, patients with advanced cancer have rated the ability to communicate effectively as a high priority (57). One indicator of this ability at the end of life is the level of consciousness before death. Consciousness is clearly influenced by a diverse range of factors, many of which are disease-specific. These factors include the rapidity of physical deterioration, coexisting organ failure, and the use of sedative medications.

A review of the mental disturbances that impact clarity of thought can shed light on the ability of patients to communicate. The occurrence of such disturbances—in particular, the occurrence of cognitive decline and delirium—in the setting of advanced cancer and toward the end of life has been specifically explored in several small studies. The 1986 National Mortality Followback Survey explored issues of orientation during the last year of life and has provided some insights into the experience of

the general population toward the end of life (11). Among the 16,000 individuals (who died of various diseases) surveyed, 61% were described as “never or hardly ever . . . having trouble understanding where he or she was during the last year of life.” Fifteen percent were described as having this difficulty for the “last few hours or days,” 13% for “some of the time,” and 8% for “all or most of the time.” Another large survey of 1227 deaths of the elderly in the United States indicated that 60% had no difficulty with orientation or with recognizing their families during the 3 days before death, and 51% had no difficulty on the day before death (30,60). No specific data about the subpopulations of cancer patients were included in the reports of these surveys.

In advanced cancer patients, the potential causes of delirium and impaired cognition may be divided into direct tumor-related effects and indirect effects (134). The latter category includes drugs, electrolyte imbalance, cranial irradiation, organ failure, nutritional deficiencies, vascular complications, paraneoplastic syndromes, and many other factors (134,135,136,137,138,139,140 and 141). Although no large, prospective survey has assessed the relative contributions of the many factors that can cause cognitive impairment in cancer patients, a survey of 140 cancer patients referred for a neurology consultation demonstrated a multifactorial etiology in most of the patients presenting with encephalopathy (141,142). The common reasons for this state were metabolic causes, drugs, and central nervous system metastases. Drugs, especially opioids, were associated with altered mental status in 64% of patients, metabolic abnormalities in 53%, infection in 46%, and recent surgery in 32%. A structural brain lesion was the sole cause of encephalopathy in 15% of patients. Although delirium improved in 67% of patients in this study, it was a poor prognostic factor for overall outcome (141). Bruera et al. studied 66 episodes of cognitive failure in 39 patients admitted to a palliative care service and cited drugs, sepsis, and brain metastasis as the most frequently detected etiological factors (143). Within this population, 22 (33%) improved, 10 spontaneously and 12 as a result of treatment. These studies demonstrate that although cognitive decline is common in the setting of advanced cancer, an active approach to the diagnosis and treatment of cognitive decline has significant benefits (143).

In the period at the very end of life, Massie et al. found that 11 (85%) of 13 terminally ill cancer patients were delirious in the immediate period before death and noted that the early symptoms of delirium were frequently misdiagnosed as anxiety, anger, depression, or psychosis (69). Recently, data from the SUPPORT study were combined with data from another group of elderly patients (total N = 4622) to evaluate aspects of the dying experience including the level of consciousness before death (58). Eighty percent of the lung cancer patients and almost 70% of the colon cancer patients in this study were reported to be conscious 3 days before death; 55% and 40% of these groups, respectively, were also reported to be able to communicate effectively at this time. A survey of 100 cancer patients who died at St. Christopher's Hospice in the United Kingdom described 10% as alert, 67% as drowsy or semiconscious, and 23% as unarousable or unconscious during the 24 hours before death (118). Finally, a survey of 154 inpatient and home care cancer patients found that one-third were able to interact 24 hours before death; this decreased to one-fifth at 12 hours before death and one-tenth in the hour before death (59).

Although these studies reveal that a high proportion of cancer patients maintain alertness until they are close to death, it is apparent that impaired cognitive functioning is prevalent, although often reversible (up until the very last days of life).

CONCLUSION

Although many studies have described the experience of patients during the advanced stages of cancer, a large number of questions remain unanswered about the physical and emotional experience of these individuals. There is a need to expand the epidemiological knowledge base particularly as it relates to specific cancers, sites of care, and aspects of the symptom experience. Information is also required about how patients are cared for and by whom; whether patients' goals for end-of-life care are being met; and which setting—home, hospital, or hospice—is most likely to meet these goals for a variety of subpopulations with differing problems and symptoms. Access to care, physicians' knowledge of palliative care, patient-physician communication, and patient-family-physician communication must be further explored. Special consideration also needs to be given to unique populations, including the pediatric, the elderly, and the mentally handicapped. Much of the distress that may occur at the end of life is responsive to palliative interventions, but a broader understanding of the many aspects of the end-of-life experience is needed for the further development of health care strategies and standards for the care of the dying. Strategies and standards must be further developed so that optimal care can be provided for all patients and families at this most difficult time.

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44

DEFINITIONS AND MODELS OF PALLIATIVE CARE

J. ANDREW BILLINGS

> Palliative care is a vast wasteland in American medicine, and nowhere is it less well understood or more neglected than in the academic health science center (1).

Palliative care clinicians face two troublesome issues in introducing themselves to a patient, family, or health care professional. First, the term “palliative care service” is still unfamiliar to many people. A simple, straightforward, concise explanation is called for, yet just a few words rarely suffice. Other specialists—for example, a cardiologist (“a heart doctor”) or an orthopedist (“a bone surgeon”)—are unlikely to be asked to define their field of expertise, nor feel challenged by the task. Second, a full explanation of palliative care necessarily refers to death, a potentially frightening topic that the patient and family, as well as the palliative care clinician, may wish to avoid, at least in the first moments of an interview. The clinician, before touching on such difficult matters as end-of-life care, wants first to listen to the patient and family (2) and understand their perspectives and information preferences, as well as to avoid saying something “wrong.” A nuanced description of palliative care services, especially for strangers facing dying, is a challenge. Phrases such as “terminal care,” “life-threatening illness,” or even “seriously ill” may stick in the clinician's mouth. One searches for euphemisms in these opening moments, yet struggles to establish a relationship that is based on authenticity and measured frankness.

To complicate this awkward situation, interpretations of the meaning of palliative care and of its scope vary within the palliative care community, reflecting the evolving nature of this not-yet-fully-formed young field. The scope of palliative medicine remains an issue for debate, ranging from absurdly broad definitions as “alleviation of symptoms,” “improving quality of life,” or treating patients “not responsive to curative treatment” to extremely narrow notions of care in the last 6 months or less of life. Discussions of definitions and standards also raise a few, significant, unsettled political conflicts about the field's future. Differences also exist across countries, and hence the focus in this chapter is on the United States, where the distinction between palliative care and hospice is an important issue. Approaches to identifying a final phase of life during which palliative care is appropriate have not been clinically useful (3,4,5 and 6). We lack elementary standards for palliative care programs—staffing, professional training of staff, eligibility of patients and families for services, scope of services, and so forth. This unfortunate state may be viewed generously as an early stage in the development of a field that still is formulating its most basic features.

Nonetheless, any description of palliative care and the hospice movement should hark back to Cicely Saunders, who developed the first modern palliative care program at St. Christopher's Hospice in London (7). She described the hospice philosophy, or hospice approach to care—skilled care that addressed physical, psychosocial, and spiritual needs of the patient and family—which forms the basis for palliative care programs throughout the world. Many current programs characterize themselves as hospices or may use the word to indicate a freestanding unit where dying persons reside and receive care, similar to St. Christopher's Hospice. The word “hospice,” however, had unacceptable connotations in French-speaking Canada, leading Balfour Mount around 1973 to coin the term “palliative care” for describing his new program at the Royal Victoria Hospital in Montreal (8), the first hospice-like unit based in an academic teaching hospital (9). “Palliative care” and the related term “palliative medicine” have become the labels of choice throughout the world for programs based on the hospice philosophy, and as discussed more fully below, are now being used increasingly in the United States (10,11,12,13,14,15,16 and 17). “Palliative care” overlaps with “terminal care,” “death-and-dying,” “hospice,” “end-of-life care,” “thanatology,” “comfort care” (18), care of “patients who may die soon and their families” (19), “supportive care” (20,21) (this term sometimes refers to comfort care, sometimes to support of the compromised host or critically ill patient, particularly those suffering adverse effects of cancer treatment), and, more recently, “hospice palliative care” (21). The diversity of meanings of these terms and their unfamiliarity to many persons can bewilder patients, family members, and colleagues in the health professions.

How palliative care practitioners label themselves, how they and others define the work, and what standards they adopt may have profound effects on the future of the hospice movement and on palliative care as a discipline. The absence of a consensus and common language among palliative care practitioners hinders progress in establishing the field. This chapter attempts to provide some clarification and to stimulate further discussion about the definition and standards for palliative care.

COMMON DEFINITIONS OF PALLIATIVE CARE

> ... the meaning of a word is its use in the language (22).

“To palliate” literally means “to cloak.” This phrase can be used to describe measures that ease suffering—that alleviate without curing—but also can connote glossing over or even giving a deceptively attractive appearance to a significant underlying problem. Thus, for clinicians, palliation can be viewed disapprovingly as merely covering up problems. Terms such as “comfort measures only” or “palliation only” suggest withholding, passivity, or giving up, whereas “best supportive care” at least suggests high quality and action. However, as currently used in American medicine, “palliative care” has become a widely accepted term for an approach to the management of a terminal illness that focuses on symptom control and support rather than on cure or life prolongation.

Anticancer treatments, such as chemotherapy or radiation, that are used to improve quality of life without an expectation of prolonging life may be described as having “palliative intent.” Interventions that were previously dismissed as ineffective in terms of survival, disease-free survival, tumor response, or performance status are now being reexamined in terms of relief of specific symptoms, psychosocial well being, functional status, and overall quality of life. Such approaches underscore the lack of clear boundaries between treatment of an underlying disease and the alleviation of symptoms. They also point to the complexity of the concept of palliation and the difficulty of assessing or measuring quality of life. As asked by Kornblith, “Does palliative care palliate?” (23) For instance, in the case of radical radiotherapy for non–small cell lung cancer, the overall outcome might reflect the patient's evaluation of the relative value of reduced hemoptysis and chest pain without an improvement in dyspnea, cough, or other symptoms, yet transiently increased general symptoms and decreased functioning and wellbeing associated with the course of radiotherapy, all with no improvement in survival or “quality-adjusted time,” and an expected general trend of deteriorating multidimensional quality of life (24).

Two widely cited definitions of “palliative care” deserve note. First, the World Health Organization, in its 1990 publication *Cancer Pain Relief and Palliative Care,* defined the term as “the active total care of patients whose disease is not responsive to curative treatment” (25).

This definition is not very helpful to patients and should be offensive to medical colleagues, who, it implies, deal only with inactive or partial care or with curative treatment! The term “active” is presumably included here to dispel notions that palliative care is passive or focused simply on avoiding interventions but seems to add little to the meaning of the definition. What is inactive care? Palliative care clinicians certainly cannot claim special expertise in the vast number of diseases that do not respond to curative treatment. Ideally, our definition should focus on the positive aspects of the work, such as helping patients and families live well or promoting their quality of life. Here, the emphasis on failure—“not responsive to curative treatment”—seems unnecessarily gloomy but perhaps is fairly gentle and acceptably euphemistic about terminal care and death. The commonly stated but problematic distinctions between palliation and curative or life-prolonging (or “life-extending”) treatment (or treatment with “aggressive intent”) are not invoked.

One strength of this definition is the assertion that palliative care should address all forms of suffering (26): “total care.” Related terms are “total pain or suffering,” “holistic care,” “total palliative care,” and “multidimensional care.” Unfortunately, such claims can sound a bit overinflated or unrealistically ambitious. “Holism” is a bankrupt term, a red light that often signals nonsense. It has lost its cachet in thoughtful social science circles (27), and the term is now regularly used synonymously with “alternative” or “complementary” medicine. Thus, holism, rather than implying a multifaceted, inclusive vision of health and illness, often stands for an unproven or idiosyncratic approach to care and a rejection of mainline medicine. A derogatory term, “symptomatologists,” has been introduced by Kearney (28) and might be used to describe caregivers who focus on various complaints and manifestations of disease but do not address the overall suffering of the person (26). “Comprehensive care” is a preferable term, especially because it already has established meaning in health services literature and avoids pretentious or confusing implications of the

other terms (29). Other characteristics of palliative care that might be related to or subsumed by the term “comprehensive” are “interdisciplinary,” “coordinated,” “integrated,” “accessible,” “case management,” “disease management,” and perhaps “humanistic” care.

This World Health Organization definition is typically followed by a longer attempt at clarification:

> Control of pain, of other symptoms, and of psychological, social, and spiritual problems is paramount. The goal of palliative care is achievement of the best possible quality of life for patients and their families. Many aspects of palliative care are also applicable earlier in the course of the illness, in conjunction with anticancer treatment.

These additional assertions are helpful, although they do not clearly distinguish palliative care from other clinical fields. Many clinicians recognize the importance of comfort and support in terminal disease as well as in nonterminal disease. Arguably, all of medicine can be viewed as seeking the goal of quality of life. Moreover, the association of palliative care solely with cancer is misleading.

A second definition of palliative care, used by the authors of *The Oxford Textbook of Palliative Medicine,* the major textbook in the field, first published in 1993, has also been widely cited:

> The study and management of patients with active, progressive, far-advanced disease for whom the prognosis is limited and the focus of care is the quality of life (30).

This definition is more concise and more precise than the World Health Organization phrases. By choosing a word such as “focus,” it avoids making palliative care a conflicting or totally separate approach from “conventional,” “curative,” “aggressive,” or “life-prolonging” measures. As discussed later, the distinction between hospice and other forms of care, as established in the United States by the Medicare Hospice Benefit, is clinically bizarre and creates a false dichotomy, suggesting that palliation can occur only in exclusion of other forms of treatment. A Canadian Palliative Care Association definition also stresses that palliative care “may be combined with therapies aimed at reducing or curing the illness, or it may be the total focus of care” (31). Indeed, palliative care must embrace all the “high-tech,” expensive, “aggressive” measures that can enhance patient and family care at the end of life (32). Certainly, palliative care should not be consigned to the final days of life when other approaches are abandoned. Moreover, as John Rowe stresses:

> Real quality of care for these [dying] patients is not more care or even less care, but the right care . . . This concept . . . doesn't rely on emerging data from molecular biology. It is not considered to be on the cutting edge by many of our faculty. But it is, in my mind, the essence of what all of us who are physicians swore when we took the Hippocratic oath (1).

The Oxford text definition also suffers from jargon and confusing terminology. What is a “limited” (or “unlimited”) prognosis? Is this designation preferable to “incurable” or “terminal?” Who will attend to the subtle distinction about the disease being both active and progressive? Where is the family in this explication?

None of these definitions is brief or clear enough to answer a patient's or family member's questions: What does palliative care mean? Or, what does a palliative care service do? Indeed, the definitions may be too abstruse and too vague even for clinicians or health care policy experts who are familiar with the jargon.

PROBLEMATIC PRECEPTS OF PALLIATIVE CARE

A variety of guidelines and positions statements on the care of the dying are available (33). The American College of Physicians–American Society of Internal Medicine has produced a set of core principles and readings (34). Definitions of palliative care are sometimes accompanied by precepts or clarifications (35,36). When viewed critically, many of these are meaningless, silly, grandiose, inappropriate for a health care discipline, or simply inaccurate. Although palliative care may be the standard bearer for some important aspects of modern medicine, particularly a focus on alleviating and preventing suffering, an emphasis on comprehensive care, and the use of interdisciplinary teams, many slogans should be quickly recognized as inappropriate for a discussion of a clinical specialty, regardless of its scope or sense of mission. Here, we should be mindful of Doyle's admonition “never to believe that we have a monopoly on care, concern, or compassion,” and of hospice's tendency to “self-righteousness” (37).

Some terms and phrases that are used in definitions or precepts—for instance, “patient-centered care,” “care *versus* cure,” “whole person care,” “treating the person, not the disease,” “compassion,” “skill,” “dignity,” “recognition of patient values,” or “culturally sensitive services”—may suggest important standards distinguishing good from bad palliative care but do not constitute essential parts of a definition. They may also imply that palliative care has a special claim on such virtues. Such terms can muddy the waters and engender misgivings from even those sympathetic to the new field. For instance, although palliative care should certainly be tailored to the needs and wishes of the patient and family, this feature does not distinguish it from other fields of medicine any more than do skill or compassion. Quality of life is a concern in all areas of medicine, and any intelligent approach to assessing quality of life begins with an understanding of patients' knowledge about their condition and potential management strategies, their values, and their personal costbenefit calculations.

The term “dignity” (as in “death with dignity”) is often used, although it seems vague and potentially laden with the care providers' values (38). As one physician reported, “I have never been particularly dignified in the sense that so many people use that word, nor have I even cared much about it. I am not sure I will want to pursue this quality when I am dying, let alone have my care significantly influenced by other caregivers' notions of what constitutes a dignified death.” Similar concerns can be raised about such terms as “develop a sense of awe,” “allow natural death,” “artifical nutrition and fluids,” “find meanings for life,” or “develop a sense of worthiness,” all of which may be appropriate goals for some patients, not for others. Nonetheless, spiritual issues, such as meaning, hope, transcendence, connectedness, and purpose, deserve a great deal of attention in palliative care services.

We also often read that hospice or palliative care “affirms life and regards dying as a natural process.” But what does it mean not to affirm life? Do other clinicians disapprove of life or truly regard dying as an abnormal process? A particular theology seems to be creeping into clinical work. Certainly, palliative care clinicians may be less likely than other clinicians to view death as a failure or as an inevitable enemy and may be more likely to see positive opportunities for growth and reconciliation in the face of dying. They also probably acknowledge dying more openly than many colleagues, but these attitudes cannot be definitions, any more than a proclivity to favor cardiac catheterization or surgical approaches for managing ovarian cancer defines, respectively, a cardiologist or a gynecologic oncologist.

Similarly, we regularly read that hospice or palliative care “neither hastens nor postpones death,” which appears to be a statement of ideology or intentions, perhaps reflecting an aversion to euthanasia or, tellingly, to life-prolonging treatment. This maxim may reflect some of the religious orientation of the hospice movement and even its distant historical background of seeking to save souls, but does not seem appropriate for defining a field of health care. Regardless, the statement has no empirical basis and does not reflect the obvious fact that hospice or palliative care practices often postpone or hasten death. For instance, patients who are eating poorly, losing weight, and becoming progressively weakened and who then receive careful mouth care, vigorous nutritional support, expert pain control, and other comfort measures are likely to live longer (and wish to keep living longer) with these palliative interventions. Likewise, vigorous application of opioid analgesics or sedatives to treat a patient's severe pain, dyspnea, emotional suffering, or terminal distress may cause drowsiness and reduced intake of food and fluids, as well as predispose to aspiration and thus potentially hasten death.

HOSPICE AND PALLIATIVE CARE IN THE UNITED STATES: A PARTING OF WAYS OR A NEW COALITION?

> Competition is greatest between those who occupy the same position in the economy of nature (39).

Hospice in the United States may be viewed as the first wave of the hospice movement. In the 1960s, volunteer hospice programs brought the hospice approach to scattered communities, focusing on home care and cancer. In the early 1980s, with the institution of the Hospice Medicare Benefit that provided funding for hospice programs, the hospice movement grew dramatically, reaching a major portion of dying cancer patients and a significant number of terminally ill persons with noncancer diagnoses. Hospice became a widely recognized feature of the health care industry. Around the turn of the century, when lengths of stay in hospice declined, the movement reached a point of possible stagnancy, leading to new ideas about promoting the hospice approach. Opportunities exist for substantial growth of hospice programs, even within the current model of care (40). Palliative care is a second wave, embracing the hospice philosophy of care—the “gold standard” for end-of-life care—and seeking to bring this approach to a wider group of patients than currently served by hospice programs in this country. Palliative care also seeks more actively to integrate the hospice approach into clinical practice rather than promoting a totally separate care system for selected dying persons and their families. Most palliative care practitioners in this country have not forsaken hospice, but rather are trying to apply the model more broadly and also more sensibly than currently fostered by federal and state hospice regulations and by health care insurance. All hospice care can be viewed as a segment of palliative care.

In the United States, hospice has come to mean specifically a governmentally regulated organization or program for dying persons and their families (1), typically focusing on home care and limited to patients with the following:

- An expected prognosis of £6 months.

- A focus on comfort measures—this is sometimes (but not always) defined by hospice programs as a desire to forego a variety of “aggressive” and often expensive management approaches (usually including cardiopulmonary resuscitation; blood product replacement; acute care hospitalization; and some forms of radiotherapy, surgery, and chemotherapy), at least insofar as these treatment modalities are being used in an attempt to cure or prolong life rather than to palliate symptoms.
- A general preference for care at home (except where inpatient hospice is available and specifically sought).
- A capacity to acknowledge that they desire a focus on comfort care, as indicated by signing an enrollment form or having the form signed by a proxy.
- Health insurance that covers hospice, unless the patient or family is willing to pay for services or the hospice program will provide free services.

Many hospice programs also require that the patient have a primary caregiver—someone to oversee care and to be readily available to the patient in the home. Typically, although not necessarily, the primary caregiver lives in the home. Other eligibility requirements, which one hears about occasionally from patients or family members but are not embodied in federal hospice regulations or the Patient Self-Determination Act, are that the patient and family agree to forego cardiopulmonary resuscitation, calls for emergency services, and/or further hospitalization.

Moreover, as documented for home care patients with amyotrophic lateral sclerosis, although hospice staff may be perceived as more knowledgeable and empathetic than conventional home care clinicians, hospice may provide fewer hours of formal care, particularly home health aide time (41). Thus, patients and families are often forced to choose between hospice care with insufficient home health aide support and a conventional home care approach that includes significantly more home health aide hours.

Hospice programs in the United States have been increasingly boxed in by the eligibility requirements created by Medicare and other insurers and by the limitations on reimbursement that make it difficult for them to cover expensive treatments or provide as much home health aide time as conventional programs (42,43,44 and 45). Many programs have become extremely cautious with admission or recertification in the face of the threat posed by an unsympathetic and perhaps ill-conceived government audit that scrutinizes long-stay patients and those with noncancer diagnoses. Hospice programs have increasingly been relegated to care in the last few weeks of life (46,47). At the same time, health maintenance organizations and insurers have attempted to “unbundle” hospice services, providing and paying for only part of the hospice package (e.g., home nursing without social service, chaplaincy, volunteers, or bereavement care).

Eligibility requirements that may make sense from a fiscal vantage in designing the hospice benefit or in running a program under the current reimbursement scheme make little sense to a clinician concerned with overall care of the dying and their families. For instance, many patients who are receiving purely comfort care and seem appropriate for hospice-like services can be expected to live for years. Many “aggressive” or “high-tech” or simply expensive interventions are appropriate for patients in the very late phases of a terminal illness and should not be foregone just to qualify for comprehensive hospice home care services. The use of antiretroviral regimens or of treatments to prevent blindness from cytomegalovirus in far-advanced acquired immunodeficiency syndrome would be common examples. Similarly, patients who may be ineligible for some hospice programs because they do not have a primary caregiver may still want to receive care at home and can benefit greatly from the support offered by hospice. Patients who need the greater home health aide hours offered by conventional home care programs and thus choose to forego hospice enrollment still may wish a palliative care approach. Patients who are aversive to the word “hospice” or who are reluctant to sign forms that redefine their insurance benefits or who have difficulty acknowledging that they are imminently facing death may benefit from and should be able to receive palliative services.

Much to the dismay of palliative care providers, hospice in the United States has become a program for imminently dying persons, caring for many patients only in the last few days or week of life (4). Only a small proportion (roughly 20%) of dying persons are cared for by hospice programs in this country. Palliative care seeks involvement with patients and families as soon as the diagnosis of a life-threatening illness is confirmed, occasionally even earlier, as commonly conveyed in Figure 44-1. Indeed, patients may present with symptoms before they have a terminal diagnosis. While undergoing curative or life-prolonging treatments, they regularly experience physical and psychosocial distress related to their underlying condition or its management. Palliative care specialists may be needed to address such distress. Palliative care is not just for the imminently dying, nor should be hospice (48).

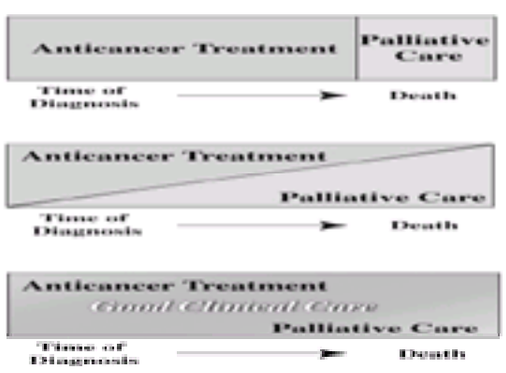

FIGURE 44-1. The top drawing depicts the common pattern of acknowledging approaching death only in the last days of life. The middle drawing depicts integration of palliative care at the time of diagnosis and increased use as the disease progresses. (After World Health Organization.) The bottom drawing conveys the lack of a clear boundary between anticancer treatment and palliative care.

In the United States, the greatest threat to hospice from palliative care would seem to be the possibility that the hospice philosophy will be distorted and supplanted by the newer programs. Palliative care teams, as a generality, differ significantly from hospice teams in this country. Hospice grew up as a grassroots, counterculture, community-based, nurse-led, and somewhat antiphysician, antiacademic movement with a strong emphasis on psychosocial care, spirituality, avoiding inappropriate interventions, using simple measures for comfort, and “letting go.” It retains much of this flavor today. Palliative care, on the other hand, is developing in academic centers and thus is “evidence-based,” centered in hospitals, and often focused on inpatient care and consultation, led by physicians who see themselves as specialists, and sympathetic to a full range of treatment options in advanced illness. Notably, none of the definitions of palliative care cited earlier in this paper includes interdisciplinary care as a basic feature. [“Interdisciplinary” in some settings is used unself-consciously to describe the collaboration of two specialists (e.g., a neurologist and oncologist) but is used here to describe the breadth of the hospice team.] Social workers, chaplains, bereavement counselors, and volunteers play an uncertain role in the future of palliative care (49). A pain- or symptom-control team that does not provide comprehensive, interdisciplinary care to patients and families may provide a needed service, but should not be confused with palliative care. Similarly, although the impact of conventional cancer treatments on quality of life and symptom control deserves much more study, palliative cancer therapy alone is not palliative care (50). Until clear standards are established for palliative care programs, including valid, professionally recognized credentialing of clinicians and accountability for standards of quality care, apprehension is inevitable that palliative care will dilute or distort the hospice philosophy and reverse the gains from the establishment of certified hospice programs in this country over the past three decades.

Hospices rightly object to terms such as “hospice-like” care because so many conventional home care programs have claimed to provide services that are equal to that of hospice but in fact do not offer many of the standard benefits of hospice, including interdisciplinary care, specially trained and supported clinicians, volunteer and bereavement services, and free medications and durable medical equipment. At the same time, some home care or hospice programs are establishing “bridge” or “prehospice” programs, paid for under conventional home care, that may facilitate early admission and avoid some of the difficulties posed by hospice admission or recertification requirements. Bridge programs represent an effort within hospice and home care organizations to extend some hospice services to patients and family that currently are not enrolled in hospice, including patients for whom conventional home care reimbursement is more favorable (e.g., for covering repeated hospitalizations or expensive interventions). These programs may also facilitate earlier and more appropriate transfers to hospice. Such bridge programs may be presented as hospice-like, but they have not been systematically studied in such a way as to assess their impact or allow a meaningful comparison with hospice care. Similar questions arise with palliative care services, which lack meaningful standards of care or accreditation of providers. Bridge programs and palliative care programs both exemplify, in part, an attempt to extend the hospice philosophy of care to more patients and families, while sidestepping the regulatory constraints of certified hospice programs, as well as the current constriction of hospice services.

Proposals from within the hospice community have attempted to deal with the limited hospice eligibility requirements. The National Hospice and Palliative Care Organization's Committee on the Medicare Hospice Benefit and End of Life Care has proposed that the 6-month prognosis requirement be eliminated and that alternate eligibility models be piloted. MediCaring (51) is an alternative program, using a hospice-like approach for patients with serious chronic illnesses.

Many opportunities remain for cooperation among palliative care programs and hospice. Briefly, hospice is generally the home care program of choice for eligible dying patients and families. Palliative care programs provide a conduit for wider education about and earlier referrals to hospice. Insofar as many palliative care services are based in hospitals, they are generally better able than hospice programs to participate in the key treatment decisions, including the transition to comfort care, which often occur in the inpatient setting. Palliative care programs tend to be based in academic institutions and can provide broader training of physicians and other health care professionals and students about good end-of-life care, which includes hospice care. Few academic palliative care programs will want to start their own home hospice programs, and most will want to work closely with hospices in a variety of communities to ensure continuity of excellent care when patients go home. Hospices

are needed as training sites for students in the health professions (52). Additionally, although a great strength of hospice in the United States has been its emphasis on quality home care and the management of chronic, progressive, fatal disease, palliative medicine can contribute to care in a variety of other settings—the acute care hospital, including the intensive care unit and the emergency ward, as well as offices and extended care facilities— and has a role in deaths from acute conditions.

Palliative Care as a Specialty

Finlay (52a) suggests distinguishing the following:

- The “palliative approach” or philosophy of care, which may be viewed as a core basis of clinical work
- “Palliative interventions” that include common approaches to alleviating suffering in clinical care and are used by many clinicians
- “Specialist palliative care,” which is the domain of clinicians with accredited training and implies minimum program and professional standards

(A similar distinction exists between the hospice approach or philosophy of care and hospice programs.) Thus, palliative care is a discipline or body of expertise and an approach to care that should infuse all medical services. Most palliative care will be provided by generalists and by specialists in established medical disciplines, such as oncology or cardiology. Some of the expertise required to provide palliative care, such as radiation therapy, interventional cardiology, or intensive care, will remain the domain of specialists in other fields. Just as a primary care physician does not need to be a cardiologist to help a patient with congestive heart failure, a clinician does not need to be a palliative care specialist to care for terminally ill persons. Conversely, cardiologists are available to clinicians and families for consultation and referral, typically for helping ensure that the best possible care is being provided and to offer specialized services. Likewise, palliative care programs and palliative medicine specialists are being developed to provide the consultation and referral opportunities that will allow for stateof-the-art care for more terminally ill patients and their families.

Much of the discussion in this chapter is meant to define specialist palliative care services, a program that helps deliver a specialized form of care. A palliative care specialist, such as a palliative medicine specialist or a palliative care nurse practitioner, is a clinician with distinctive training in this field who works in conjunction with a specially trained, interdisciplinary palliative care team. A large literature documents unmet needs of terminally ill patients and their families, as well as a lack of expertise of both generalists and specialists in meeting these needs (16,17,53,54,55 and 56), so a case can easily be made for a separate discipline of palliative care that entails such features as the following:

- Diagnostic and management skills and the ability to act as a consultant to other clinicians for a multitude of illnesses and complex conditions, including syndromes that are usually seen only in the late phases of an illness
- Expertise in the pharmacological basis for alleviating suffering, as well as in nonpharmacologic approaches
- Communication skills—widely recognized as challenging and beyond the everyday competency of most clinicians—that reflect expertise in the psychological, social, and spiritual aspects of care for patients and families, including bereavement care
- Caring for seriously ill patients in the home or other alternatives to the acute care hospital
- Team care
- Educating generalists and other specialists about palliative care
- Conducting research in palliative care

As a fledgling field, palliative care now can boast of multiple clinical centers and training programs; a variety of fine textbooks (57), journals, and educational conferences; and a small research enterprise. A recent Supreme Court ruling on legalization of physician-assisted suicide has been interpreted as acknowledging a right to “good palliative care.” The Institute of Medicine report (1) reviewed the difficult question of whether palliative medicine should become a specialty or an area of exceptional competence within existing fields but did not make a firm conclusion. Certainly, the justification for a new field would include an ability to address unmet patient and family needs, offer expertise with difficult cases and unfamiliar treatment methods, train medical students and graduate physicians, and carry out research.

Palliative medicine has been recognized as a specialty in the United Kingdom since 1987, in Australia and New Zealand since 1988, and more recently in Canada. A variety of criteria have been cited as the requisites for identifying a distinct discipline: “a defined need, a separate and specific body of knowledge, skills, and attitudes, a shared set of principles, public acceptance, defined standards of practice, a literature devoted to the field and a research base” (58). In the United States, some discussion about principles may still exist, but standards of practice are clearly lacking.

Many of the values and skills embodied in the notion of palliative care are more readily identified with generalist or primary care practice than with specialist or consultive practice. If palliative care practitioners are specialists, they **cannot** delineate their work as the following:

- Organ- or organ-system based (e.g., nephrologists principally take care of the kidney, neurologists the nervous system),
- Disease-based (e.g., oncologists principally take care of cancer), or
- Age-based (e.g., pediatricians provide general medical care to children)

However, palliative care is end-of-life care, directed to dying persons and their families at all phases of terminal illness. It cannot be a subset of oncology or any other subspecialty because palliative care deals with every failing vital organ and a variety of diseases occurring at all ages. Similarly, although palliative medicine may be developing primarily as hospital consultation service (12) and might be viewed as an inpatient specialty, analogous to “intensivists” or “hospitalists,” the bulk of patients requiring palliative care are outpatients. A focus only on institutional care would undermine a comprehensive approach and contribute to further fragmentation of end-of-life care.

Palliative care practitioners, then, are like generalists, providing comprehensive, accessible, first-line care, but only to a subset of patients and their families—those facing a terminal illness. This approach is similar to how geriatricians may define themselves as generalists for the elderly.

Regardless of the orientation of palliative care practitioners as specialists or generalists, they need to interface effectively with patients, families, and health care providers who have a variety of needs, wishes, and resources. They need to work closely and comfortably with clinical colleagues who provide the bulk of preterminal care. For instance, when a skilled, dedicated primary care provider is managing a case, the palliative care practitioner might act solely as a consultant, providing advice directly to the referring physician. Only part of the palliative care team—for instance, the social worker, chaplain, or volunteer—might become directly involved with the patient or family, complementing the work of the primary care doctor. On the other hand, if the patient is being followed, for instance, by a neurosurgeon who views his or her job as largely completed after recovery from surgery, patients, families, and health care providers may prefer that the palliative care team assume a primary care role, taking responsibility for not only the management of the terminal illness but also for coordinating the input of the specialists, ensuring good communication and overseeing general medical management. For a patient undergoing chemotherapy or radiation for a cancer, care might be comanaged with the oncologist or radiation therapist; the palliative care clinician would share some responsibility for symptom management but perhaps take a dominant role in supervising home care services or providing psychosocial and spiritual support.

From this perspective, palliative care in the United States must be flexible and collaborative (59), yet retain responsibility for ensuring coordination of comprehensive care and at times providing a full range of appropriate services. Palliative care programs must have the capability of offering a range of consultative and primary care services. A simple consultative approach that focuses on symptoms, particularly physical symptoms, without addressing broader psychosocial and spiritual aspects of patient and family suffering—exemplified by some pain services or pain and symptom control teams—is neither state-of-the-art symptom control nor true palliative care.

A few arguments against establishing a separate specialty of care deserve note. One concern is that terminally ill persons will become recognized as a distinct class of patients who are referred to specialists, thus reducing the skills of generalists and other clinicians in the care of these patients and isolating the patients from their usual health care team. Second, most of the needs of the dying are shared with other patients with “life-threatening and complex” diseases, and a smarter approach to reforming the health care system would embrace these constituents.

TYPES OF PALLIATIVE CARE PROGRAMS

In the United States currently, palliative care programs can be divided into those that are covered under a hospice benefit and those, generally labeled as palliative care programs, that rely on conventional channels of reimbursement and possibly also hospice reimbursement. Programs can also be divided up according to the sites in which care is offered and whether staffing at the site is provided by a dedicated hospice/palliative care team or by usual staff in consultation with such a team.

For state and federal certification, hospice programs are obliged to provide both home care and acute inpatient care. Home care may include nursing home care, and indeed, some hospices provide primarily nursing home care. Residential facilities or boarding houses run by hospice programs may provide home care in a special setting where the hospice benefit is used to pay for medical-nursing services, whereas room and board is covered by the patient or sources other than health insurance. Home care under hospice may include brief periods of “continuous care,” which involves around-the-clock presence of nurses or home health aides address a need for more intensive service. Respite care, typically offered in a nursing home setting, may also be available. Acute inpatient care may be provided in scattered

hospital beds; in a dedicated inpatient unit located in a hospital, extended care facility, or nursing home; or less frequently, in a free-standing inpatient unit. Acute hospital days under hospice generally constitutes a small fraction (<5%) of the total days in hospice. Rare hospice programs in this country offer day care.

Palliative care programs in this country may assume similar configurations as provided under the hospice benefit but now generally consist of inpatient consultation teams, dedicated inpatient units of various sizes in acute care hospitals or extended care facilities, ambulatory care clinics, and specialized home care programs (including "bridge" services affiliated with a hospice). Eligibility for services tends to be much broader than under the Medicare Hospice Benefit but may include less attention to psychosocial and spiritual issues or home care.

Most care in hospice is provided in consultation with and under the orders of a primary care physician, although a hospice medical director or other hospice physician may direct care in some programs. In palliative care, the option for primary care management of patients also exists.

ELEMENTS OF A DEFINITION

Palliative care is characterized by the following:

1. Focusing on a particular clinical condition: *terminal illness* or *end-of-life care.* Unlike hospice in this country, the field does not need to specify a prognosis. In describing itself as caring for the dying, euphemisms should be avoided, but a definition need not be so blunt as to frighten patients and their families (e.g., speaking about "incurable" or "terminal" disease) nor be so kindly as to become hopelessly vague (e.g., describing patients as "advanced"). For health care colleagues, *"terminal illness"* or *"end-of-life care"* are relatively clear notions and allow flexibility to participate in the earlier phases of "active, progressive" fatal conditions that eventually become "far-advanced." For patients and families, *"life-threatening illness"* may be the most appropriate and acceptable descriptor, although this term includes conditions, such as acute trauma, that are not typically within the palliative care domain.
2. Employing a distinct method of evaluation and management, a special expertise:

   - *Comprehensive* (meaning addressing all forms of suffering)
   - Interdisciplinary (or collaborative) care

The terms are included here because of their importance in distinguishing the mission of this field. Admittedly, most clinical disciplines do not specify a method of care except for the implied distinction between medical and surgical specialties. Within a field, we may hear about a "minimally invasive surgeon" or an "interventional radiologist," but all palliative care is comprehensive in scope and interdisciplinary in practice.

3. Directing care to the *patient and the family* and, by implication, extending care into the period of bereavement.
4. Focusing on a specific management goal: *promoting quality of life* (or *alleviating and preventing suffering* or, particular for patients and families, *living as well as possible*). This goal need not exclude other goals, including cure or remission. MacDonald summarized this concept nicely as a fourth phase of cancer prevention (60). Alternative terms that may be more acceptable to patients and families are *"comfort care"* or *"supportive care,"* although the former tends to imply passivity and withholding, as suggested by "comfort measures only," whereas the latter is regularly used to designate treatments clearly aimed at prolonging or sustaining life.

Hence, palliative care is comprehensive, interdisciplinary care for patients living with a terminal illness and for their families, focusing primarily on promoting quality of life. Key elements for helping the patient and family live as well as possible in the face of life-threatening illness include ensuring physical comfort, psychosocial and spiritual support, information sharing and establishing a treatment plan reflective of patient values and goals, and provision of coordinated services across sites of care.

This explication does not mention anything about supporting the service providers, an essential feature of any palliative care program, yet one that does not seem to deserve inclusion in a brief definition statement. The definition also does not specifically address the components of an interdisciplinary team and, like other definitions above, does not specifically mention volunteers or bereavement services.

WHAT DO YOU SAY?

For statements that are intended primarily for clinicians and other health professionals, I speak of "comprehensive care, provided by an interdisciplinary team, for patients and families living with a life-threatening or terminal illness, particularly where care is focused on alleviating suffering and promoting quality of life." I might then go on to clarify:

> Major concerns are pain and symptom management, psychosocial and spiritual support, information sharing, and advance care planning to address patient values and goals, and coordination of care across multiple sites, including arranging for excellent services in the community.

In talking with patients as a consultant, I might say:

> Palliative care is a special service we offer, a team approach to providing the best care and support for persons living with a life-threatening illness and for their families. Our goal is to help you live as well as possible with your condition. We are a nurse, social worker, chaplain, and physicians who work with your current health care team to ensure, insofar as you need it, that you and your family have access to excellent pain control and other comfort measures, get the information you want to participate in decisions about your care, receive emotional and spiritual support and practical assistance, obtain expert help in planning for care outside the hospital, continue getting good services in the community, and overall enjoy life as best you can, given your illness. We try to coordinate and tailor a package of services that best suits your values, beliefs, wishes, and needs in whatever setting you are receiving care.

STANDARDS

Discussions about definitions, philosophies, or precepts can be useless if not translated into meaningful, robust standards of practice. Two kinds of standards are commonly applied: program standards, which describe the organization and delivery of palliative care services, and professional standards, which apply to the training and skills of members of the palliative care team.

Program Standards

In hospice, Medicare regulations provide guidance about hospice eligibility, as described above, but also identify the members of the interdisciplinary team, prescribe regular team meetings, and indicate how services are reimbursed (61). As scant as these regulations may seem, they may be seen as generally successful in establishing standards for hospice programs. No standards of this sort exist for palliative care programs in this country. This means that anyone can use the term "palliative care service" to describe a program, and that patients, families, clinicians, administrators, regulators, and policy makers have no guarantee of a minimal standard of service when referring to such a program.

A remarkable process for developing standards has been initiated by the Canadian Palliative Care Association (62,63 and 64), and is available on-line at http://www.cpca.net. Sections include a lexicon of key terms, a statement of values, and a highly detailed listing of principles and norms for a variety of program features. Under Assessment, for instance, the document describes a principle of comprehensive and timely evaluation and describes such norms as respecting confidentiality; identifying and prioritizing patient expectations and needs; and assessing religious values, beliefs, and practices.

Professional Standards

No meaningful standards exist for professional participation in a hospice or palliative care program. Anyone with a medical license can serve as a hospice medical director. Certification programs in medical and nursing aspects of palliative care (the American Board of Hospice and Palliative Medicine, the Palliative Care Nursing Society) have been developed but hold little face value. The American Board of Hospice and Palliative Medicine, after certifying roughly 800 physicians, has committed itself to revising its examination procedure to conform better to current standards of educational testing. The board has also outlined a process for establishing palliative medicine as a recognized medical specialty that would eventually include a requirement for fellowship training to become certified.

Do definitions and standards matter? A few examples drawn from "real life" suggest some of the issues:

- A pathologist with a deep commitment to end-of-life care but no clinical training after medical school becomes a hospice medical director.
- A long-standing palliative care program in a predominantly rural region has never had a medical director, regular physician oversight, or even routine

opportunities for the clinical staff to obtain medical consultation on their patients.
- An academic palliative care program includes no regular participation from the chaplaincy and provides no organized bereavement services.
- One clinical fellowship program in palliative care enrolls only cancer patients, whereas another serves only patients and families who meet the admission requirements for hospice in the United States.

CONCLUSION

Throughout the world now, palliative care is developing as an area of special clinical competence and is growing rapidly in the United States (65). Palliative care has attracted clinicians from disparate backgrounds and interests, and hence the field currently embraces a diversity of views about its scope, goals, and methods. This diversity is a virtue. Where different viewpoints and expertise are shared, cross-fertilization occurs, and untested assumptions are challenged. However, diversity implies disagreement or conflict within the field and hence confusion for those trying to understand it. Diversity currently also means lack of meaningful standards. The challenge today for palliative care is to avoid orthodoxy, yet move ahead with greater unanimity about the nature of the field and with improved standards for palliative care professionals and programs.

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HOSPICE

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> Not every patient can be saved, but his illness may be eased by the way the doctor responds to him—and in responding to him the doctor may save himself. But first he must become a student again; he has to dissect the cadaver of his professional persona; he must see that his silence and neutrality are *unnatural*. It may be necessary to give up some of his authority in exchange for his humanity, but as the old family doctors knew, this is not a bad bargain. In learning to talk to his patients, the doctor may talk himself back into loving his work. He has little to lose and everything to gain by letting the sick man into his heart. If he does, they can share, as few others can, the wonder, terror and exaltation of being on the edge of being, between the natural and the supernatural.
>
> —Anatole Broyard, *Intoxicated by My Illness* (1)

HISTORY OF HOSPICE

The modern hospice movement began in 1967 in London under the direction of Dame Cicely Saunders, with the opening of St. Christopher's Hospice. Saunders emphasized the need for effective symptom control, the care of the patient and family as a unit, and the interdisciplinary team approach. Treatment approaches included the continuum of care, the use of volunteers, and follow-up with family members after the death of the patient. Dr. Saunders introduced the concept of applying research to the care of the dying and developed the idea of giving pain medication around the clock rather than by request. In addition to the remarkable achievements of Dr. Saunders, fellows and students from St. Christopher's hospice have contributed significantly to the development of hospice and palliative care programs around the world (2). Dr. Robert Twycross developed the World Health Organization's Collaborating Center for Hospice/Palliative Care in Oxford. Dr. Balfour Mount opened the Palliative Care Service at the Royal Victorian Hospital in Montreal in 1975. Florence Wald, Dean of the Graduate School of Nursing at Yale University, opened the New Haven Connecticut Hospice in 1974: the first hospice home care program in the United States without an inpatient service.

Economic forces have shaped the location of death in the United States, while cultural forces have influenced the acceptance and understanding of death. The hospice movement began at a time when Elisabeth Kübler-Ross was developing her theories on death and dying. Death was occurring in impersonal modern institutions where increasingly technologic and life-sustaining measures were the main focus of medical care. The hospice movement began in part as a reaction to and against the impersonalization of dying. A major factor in the growth of the hospice movement in the United States was the perception by nurses, patients, and families that the traditional medical care system failed to meet the needs of the dying patient (3). Hospice developed more as a concept of care rather than a place for care. From the beginning, the focus has been on care in the patient's own home.

In 1974, the National Cancer Institute funded the Connecticut Hospice in New Haven, the first home care–based hospice in the United States. This demonstration center provided home care for terminally ill patients and their families. Subsequently, hospices were funded through grants and private donations, and relied heavily on lay and professional volunteers (4).

A Health Care Financing Administration hospice demonstration program was initiated in 1980. In 1982, Congress passed the Tax Equity and Fiscal Responsibility Act, which authorized Medicare to reimburse hospices for the care of terminally ill patients who met specific criteria. This marked the birth of the Medicare Hospice Benefit (MHB), which would define hospice care in the United States and become the first federally mandated, managed-care program in the country. Reimbursement by Medicare and other insurance programs was supported in part under the assumption that hospice care would replace hospital inpatient care and theoretically be less expensive. A stipulation was added to the MHB that 80% of hospice patient care days per certified agency, per year must be used for home care.

HOSPICE PHILOSOPHY

The modern hospice movement focuses on the multidimensional symptoms of the patient and the family rather than only on the terminal disease. Beyond controlling symptoms, hospice enables the patient and family to confront the issues that accompany approaching death. The emphasis on “Total Pain” from sources including physical, psychological, social, and spiritual exemplifies hospice care. Pain management and management of other nonpain symptoms, such as anorexia, nausea, fatigue, anxiety, and depression, often allow other sources of pain or suffering to surface. The focus of care is individualized to meet patient and family needs.

As supported by the World Health Organization, the philosophy of hospice care for the terminally ill is based on several concepts (5).

1. Death is a natural part of the life cycle. Hospice will not seek to hasten death or to postpone it.
2. Pain relief and symptom control are clinical goals.
3. Psychological and spiritual pain is as significant as physical pain, and addressing all three requires the skills and approach of an interdisciplinary team.
4. Patients, their families, and loved ones are the unit of care.
5. Bereavement care is critical to supporting surviving family members and friends.
6. Care is provided regardless of ability to pay.

A primary goal of hospice and palliative care is to promote an alert, dignified, and pain-free life for its patients in a manner that is respectful of their individual needs (6).

Hospice emphasizes the coordinated approach to care as a means to enhance the combined skills of caregivers. The approach is comprehensive and case managed. Frequency and types of visits are determined by the needs of the patient and family or caregivers. Psychosocial and spiritual support and counseling, to cope with the significant challenges and crises, are reviewed as the illness progresses. The core members of the hospice team include

1. The patient's attending physician
2. A hospice medical director
3. Nurses with advanced training in end-of-life clinical care
4. Social workers with clinical experience appropriate to the counseling and casework needs of the terminally ill
5. Spiritual counselors with education and experience in pastoral counseling
6. A volunteer coordinator with skills in organization and communication
7. Trained volunteers

Additional professionals (therapists, dietitians, pharmacists, and nursing assistants) may join the team as needed. The team collaborates on an ongoing basis with the patient's attending physician to develop and maintain a patient-directed, individualized plan of care. This plan addresses the multidimensional nature of patient and family needs. Hospice seeks to address factors considered important at the end of life by patients and family members. Pain and symptom management, communication with one's physician, preparation for death, and the opportunity to achieve a sense of completion are important to most patients (7).

There is evidence that particular aspects of the dying process are areas of concern to patients. Patient-clinician relationships, social connectedness, caregiving needs, psychological distress, spirituality/religiousness, personal acceptance, sense of purpose, and clinician communication are all areas of concern for patients near the end

of life (8). Attention to these aspects are of primary importance in the interdisciplinary approach to care.

Hospice emphasizes the need to empower families and considers bereavement a critical component of supporting surviving family members and friends. Services related to bereavement continue for at least 1 year to help the family cope with death-related grief and loss. Survivors with potentially pathological grief reactions or complicating comorbidities may be referred for appropriate counseling services.

MEDICARE HOSPICE BENEFIT

The MHB has had a major influence on the evolution of hospice and has served as a model for private insurance companies. It defines when and how care will be delivered, by whom it will be delivered, and to whom it will be delivered. In addition, it specifies a payment structure for reimbursement (Table 45-1, Table 45-2).

The patient must be terminally ill, with a life expectancy of 6 months or less if the illness runs its usual course. Two physicians, the patient's attending physician and the hospice medical director, must attest to the terminal nature of the illness.
The Medicare Part A hospice benefit, when elected, precludes all other Medicare benefits related to the terminal illness except for the professional services of the attending physician. Care is coordinated through the hospice.
The benefit consists of two periods of 90 days, followed by an unlimited number of benefit periods of 60 days each. Prior to each benefit period, the hospice medical director must recertify that the patient has a prognosis of 6 months or less if the disease runs its usual course.
The patient may revoke the hospice benefit at any time. Normal Medicare Part A benefits are immediately restored.
Certified Medicare hospice agencies are reimbursed on a per-diem basis, depending on the level of care provided.
Routine home care
Continuous home care (brief periods of medical necessity, minimum of 8 to 24 hours per day)
Respite care (maximum of 6 consecutive days)
Inpatient care
At least 80% of hospice program days per year, per agency, must be categorized as routine home care.
An annual payment cap is placed on each hospice program based on the number of enrolled patients.

Adapted from Kinzbrunner BM. The terminally ill patient. In: Abeloff, ed. *Clinical oncology*, 2nd ed. Churchill Livingstone, 2000:597–623, with permission.

TABLE 45-1. MEDICARE HOSPICE BENEFIT

Nursing services
Medical social services provided by a social worker under the direction of a physician
Physician services to provide palliation and management of the terminal illness
Counseling
Bereavement up to 1 yr after the death of the patient
Spiritual—provided by clergy
Dietary if needed
Other—as needed
Physical, occupational, and/or speech therapy if indicated
Laboratory tests and diagnostic studies related to the terminal illness
Home health aide services
Homemaker services
Medical supplies
Drugs and biologicals
Durable medical equipment
Other medical supplies

Adapted from Kinzbrunner BM. The terminally ill patient. In: Abeloff, ed. *Clinical oncology*, 2nd ed. Churchill Livingstone, 2000:597–623, with permission.

TABLE 45-2. SERVICES COVERED ON A PER-DIEM BASIS BY THE MEDICARE HOSPICE BENEFIT.

COST CONCERNS

Medical care at the end of life has consumed 10–12% of the total health budget and 27% of the Medicare budget (9). There have been controversy and confusion over how much money if any can be saved by provision of hospice care to terminally ill patients. Actual cost savings estimates for hospice care over traditional care vary, but an estimate is 25–40% during the last month or less of life, 10–17% during the last 6 months, and from 0–10% if the patient is enrolled in hospice during the last 12 months of life (10). These estimates are derived from data limited by methodological issues of selection bias, time-frame differences, types of medical costs evaluated, variability of reporting, and lack of generalizability. It is possible that some of the savings realized result from a shift in costs and burdens to the caregivers rather than costs for hospitalization or higher levels of care.

HOSPICE IN MAINSTREAM MEDICINE

In the United States, approximately 20% of deaths occur with hospice, and 42% of patients have diagnoses other than cancer (11). Nationally, 78% of hospice patients are 65 or older, 55% are female, and 38% are nonHispanic white. Hospice care remains underutilized as a resource for those with advanced, ultimately fatal illness (12).

The movement that began as a revolution against impersonal end-of-life care has become increasingly mainstream with the legitimacy of specialty societies, reimbursement mechanisms, and the development of a substantial body of knowledge. Many third-party insurers include hospice care as a benefit, as does Medicare. The Department of Veterans Affairs mandated hospice services provided directly or through community referrals in 1991. This position was reaffirmed in the Millennium Bill of 2000 (13).

Hospice in mainstream medicine faces many challenges. The first challenge is related to the definition of terminal illness. Palliative care can no longer be reserved for those facing imminent death. Many are concerned that hospice care should not be limited to patients during the last 6 months of life and that patients could benefit from even earlier enrollment. The developing field of palliative medicine is beginning to address the need to provide comprehensive interdisciplinary care for patients not only in their last 6 months of life. It can encompass interdisciplinary care to alleviate suffering at any point along the trajectory of the illness. Most palliative care services, however, are provided in acute inpatient settings, in part due to Medicare reimbursement mechanisms and limitations on prospective home health care. Hospices are moving toward this broader model of palliative care in order to avoid the dichotomy of choosing between curative and supportive therapies. Perhaps the disease that best illustrates this concept is congestive heart failure. According to National Hospice and Palliative Care Organization prognostic guidelines, the same treatments used to optimally treat the disease are identical to those used in the palliation of symptoms.

A second challenge relates to the definition of "6-month prognosis." As written, the MHB is unclear regarding what percentage of patients should be expected to die within the 6-month period with a given disease (14). In reality, hospices have been the target of focused review to determine if admissions to hospice were indeed appropriate, with the accusation of fraud if patients lived beyond their predicted life expectancy. Patients increasingly appear to be enrolled closer to the time of death. The average period of hospice care fell from 74 days in 1992 to 59 days in 1998. Greater federal scrutiny of compliance with program eligibility requirements may have contributed to a decline in beneficiaries' average number of days of hospice care (15).

The National Hospice and Palliative Care Organization developed guidelines for patients with diseases other than cancer that might be considered appropriate for hospice care, listed in Table 45-3.

Condition	Criteria
Heart disease	NYHA IV, EF <20%, refractory to optimal treatment including vasodilators. Other factors suggesting poor prognosis: symptomatic arrhythmias resistant to antiarrhythmic therapy, history of cardiac arrest, unexplained syncope, cardiogenic brain embolism.
Pulmonary disease	Disabling dyspnea at rest, FEV_1 <30%, frequent emergencies, cor pulmonale, hypoxemia on O_2, hypercapnia, resting tachycardia, unintended weight loss.
Dementia	Bed or chair bound, dependent in activities of daily living, incontinent, unable to communicate beyond six meaningful words, severe medical comorbidities, nutritional compromise, tube feedings refused, or impaired nutrition on tube feedings.
Stroke	Acute phase, beyond 3 d: coma, abnormal brainstem response, absent verbal response, absent withdrawal to pain. Dysphagia precluding nutrition when artificial feedings refused. Poststroke dementia, Karnofsky score ≤50%, nutritional compromise. Recurrent aspiration pneumonia, urinary infection, sepsis, decubitus ulcers.
Renal disease	Meets criteria for transplant or dialysis but refuses; C_{cr} <10 mL/min, serum creatinine >8 mg/dL (6 mg/dL for diabetics).
Liver disease	Not considered for transplant, albumin <2.5 mg/dL, prothrombin time >5 sec over control, recurrent variceal bleeding, cachexia, alcohol use. At least one of the following: refractory ascites, SBP, hepatorenal syndrome, hepatic encephalopathy, coma.

C_{cr}, creatinine clearance; EF, ejection fraction; FEV_1, forced expiratory volume in 1 sec; NYHA IV, New York Heart Association Stage IV; SBP, spontaneous bacterial peritonitis.
From Robinson BE. Assessment in special settings. In: *Handbook of geriatric assessment*. Gaithersburg, MD: Aspen Publishers, 2000:314, with permission.

TABLE 45-3. NATIONAL HOSPICE ORGANIZATION GUIDELINES FOR PROGNOSIS IN CHRONIC DISEASES

A third challenge that hospices face is the tyranny of numbers. Many smaller hospices are unable to offer technologically advanced or nonpharmacological diseaserelated treatments. In theory, large hospices, by virtue of higher average daily census, are better positioned to offer more costly or technologically advanced care. This care might be offered on a trial basis for effect or a permanent basis depending on the indications. In contrast, smaller hospices have difficulty financing expensive “palliative” treatments, such as total parenteral nutrition, palliative surgery, or chemotherapy.

Site of care presents another barrier to accessing hospice care. The provision of Medicare hospice services to nursing home residents has come under scrutiny by the Office of the Inspector General. It is a source of conflict among hospices, nursing homes, and payer sources or fiscal intermediaries. Currently, the Office of the Inspector General estimates that only 1% of nursing home residents elect the MHB (16). Many hospices have been advised not to provide care for nursing home residents receiving care under the Medicare Skilled Nursing Home Benefit even in a private-pay category. The fear of appearing as potentially inducing referrals for accessing the MHB once the patient is off the Skilled Nursing Home Benefit. Nonetheless, nursing home residents receiving hospice services can benefit greatly from hospices' expertise in providing palliative management of the dying patient's symptoms, attending to increased hygienic needs, and supplying bereavement services to family and staff (17). The interdisciplinary hospice team can serve a continuity-of-care function for the patient admitted from home, or for hands-on care in a setting where staff turnover is high. Recent studies revealed improved care and fewer hospitalizations among terminal nursing home patients when their care was augmented with hospice services (18,19).

MINORITIES AND SPECIAL POPULATIONS

Access to hospice care for the pediatric population is limited. Only 247 of 2500 hospice programs have programs specifically for children (20). Many families are not ready to accept a life-limiting prognosis given to their child. In addition, the problem of estimating prognosis may be more difficult in this population, particularly with diseases from which cure is possible or even likely. Hospice programs may require that the patient forgo potentially curative or life-prolonging therapies or not offer high-tech services such as ventilator support or chemotherapy. Differentiating between lifeprolonging therapy and symptom-management–directed therapy may be quite difficult in this population. Recently, the American Academy of Pediatrics issued care guidelines for children with life-threatening and terminal conditions to address some of these issues (21).

The prison system presents another challenge to hospice programs. Since 1987, the number of people dying in prisons has increased more than 100%, from 1400 to over 3200. There are currently 1.83 million men and women incarcerated in 1515 prisons throughout the United States facing the threat of inadequate medical care. To compound this crisis, there are only 26 prison hospice programs in the United States capable of handling increasing incidences of AIDS, tuberculosis, and other chronic illnesses that have put an enormous burden on the prison system. In addition, suicide remains one of the highest causes of death in jails— nine times the national yearly average (22). In many instances, prison facilities are not capable of delivering proper health care, especially in the inmates' final months of life. Dying inmates desperately need access to pain and symptom control and psychological counseling during the final stages of their lives. The first-ever national conference on death and dying in U.S. prisons and jails, sponsored by Project on Death in America and The Center on Crime, Communities & Culture, took place in 1998 at the New York Academy of Medicine.

HOSPICE EDUCATION

The American Board of Hospice and Palliative Medicine (ABHPM) was founded in 1995 to establish and implement standards for certification of physicians practicing hospice and palliative medicine. The board held its first certifying exam in 1996. In addition, the American Academy of Hospice and Palliative Medicine was accepted as a provisional member of the Specialty and Service Society Section of the American Medical Association in 1996. In 2001, a fellowship membership category of the American Academy of Hospice and Palliative Medicine was established (23). To date, the ABHPM has certified 835 U.S. physicians and is engaged in discussions with the American Board of Medical Specialties ultimately to establish a subspecialty of hospice and palliative medicine. Fellowship programs in palliative medicine are expanding within the United States with over 30 programs currently available. Currently, the ABHPM is developing common standards for palliative care fellowships.

FUTURE OF HOSPICE

The current health care financing system is ill equipped to deal with the reality of how most Americans die. Although people still succumb to acute illness and trauma, far more die of chronic progressive disease from which a cure is not possible. Hospices have recognized the need to care for these patients and some are moving toward offering hospice (end-stage) services as well as palliative (symptom-controlling) therapies earlier in the disease process. It could be argued that palliative care services should be a part of any illness therapy from the time of diagnosis to death, with palliative and hospice services occupying a larger focus as the disease progresses.

The current system encourages acute over palliative care and often fragments care between systems. Medicare tends to foster inpatient care and poorly supports home and community-based care outside of hospice. It is often easier to arrange a hospitalization than to arrange for personal care or a home-delivered meal for a seriously ill patient. Following the hospice model, organizations, such as Americans for Better Care of the Dying and the Institute for Health Care Improvement, are calling for better care of the dying and those with chronic illness through education, research, and advocacy.

To the credit of hospice pioneers and supporters, the evidence base for the possibility of dying with symptom control, spiritual attention, psychosocial support, and attention to caregivers, is mounting. The movement that began in part as a revolution against the cold impersonal manner of dying may yet change the face of dying, not only for those identifiable as having a “six-month prognosis” but for all of those facing life-limiting illness at any stage. Hospice is hoping to see Medicare change its reimbursement system for care near the end of life to improve access for those in need. It has allowed death and dying to be an increasing part of mainstream medicine, and it continues to try to expand its services to those who can benefit from care.

RESOURCES

Organizations

American Academy of Hospice and Palliative Medicine

4700 W. Lake Ave., Glenview, IL 60025-1485 847/375-4712

www.aahpm.org

Hospice Foundation of America

2001 S St. NW, Suite 300, Washington, DC 20009 800/854-3402

www.hospicefoundation.org

International Association for Hospice and Palliative Care

Liliana De Lima, Executive Director

UT M D Anderson Cancer Center

1515 Holcombe Blvd. Box 08, Houston, Texas 77030 713/339-2006

www.hospicecare.com

National Hospice and Palliative Care Organization

1700 Diagonal Road, Suite 300, Alexandria, VA 22314 703/837-1500

www.nhpco.org

Internet resources:

Americans for Better Care of the Dying, www.abcd-caring.org

Center to Advance Palliative Care, www.capcmssm.org

Education for Physicians on End of Life Care, www.epec.net

End of Life Physician Education Resource Center, www.eperc.mcw.edu

Growth House, www.growthhouse.org

Institute for Healthcare Improvement, www.ihi.org

MediCaring, www.medicaring.org

National Association for Home Care, www.nahc.org

Project on Death in America, www.soros.org/death

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MULTIDIMENSIONAL PATIENT ASSESSMENT

J. CAMERON MUIR
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From the earliest times in medicine, there has been a signifi-cant emphasis on the relief of suffering. As Hippocrates said, “I will use treatment to help the sick” and “to help, or at least to do no harm” (1). From the time of Hippocrates (~500 BC) through the nineteenth century, the focus of health care has been the relief of suffering associated with injury and disease. However during the last half of the nineteenth century and into the twentieth century, health care has become almost entirely focused on the *disease* and has often neglected to care for the *person*. As a result, the disease has been treated while the suffering that the patient is experiencing is often left unaddressed. It has only been during the past two decades that there has been a resurgence of the ethic of pal-liative care. This resurgence is most likely due to recognition of the limits of the current curative model of care. Although we have become more proficient at staving off death, it still will occur 100% of the time (2). It is through a skilled mul-tidimensional patient assessment (MDPA) that the various elements of suffering can be identified and addressed, from diagnosis of a cancer, through treatment, and into remission, disease progression, and death.

In this chapter we will review the components of a mul-tidimensional patient screening and assessment, which is often also referred to by the patient/family as “holistic or whole person” care. Particular emphasis will be placed on the role of an interdisciplinary team and a distinction will be made between the traditional “medical model” and the interdisciplinary “bio-psychosocial-spiritual model” of care, which is so well modeled in the field of hospice and pallia-tive care. The different components of the MDPA will then be described with particular emphasis on knowing how and when to integrate other disciplines' skills and assistance.

INTERDISCIPLINARY ASSESSMENT

There is a growing appreciation that a patient's experience of his or her advanced illness is complex: from physical symptoms, to coping, financial concerns, caregiver burden, social/family changes, and spiritual concerns. Furthermore, no one person—regardless of his or her professional disci-pline— will be able to manage all of these issues (3,4 and 5). In fact, attempts to do so may result in either harm to the health care provider through exhaustive efforts to deal with everything alone, leading to stress and burnout (6,7), or harm to the patient and family, because the health care pro-vider either completely misses an issue due to lack of skill in that area, or by trying to do something that he or she is not adequately trained to do.

Each health care discipline has expertise and skills in providing care to the patient and family and in identifying their specific needs and clarifying goals of treatment within a holistic framework. One might ask, “What discipline is most appropriate for performing an initial assessment?” Although there are few data to support an answer to this question, there is some anecdotal evidence from evaluation of the systems currently in place and what seems to work. There are two predominant models of care provided in health care: the traditional “medical” model and the interdisciplinary/palliative care model. There are significant differences between the two models of care (8,9).

The traditional medical model is the predominant model of health care and can be characterized as disease focused, with the physician as the leader. Physicians run most ambulatory clinics that see patients with “problem lists” and “chief complaints”; a history is taken, and then a physical examination is performed. Based on clinical findings, patients undergo diagnostic testing in an attempt to reveal a diagnosis for which some form of therapy is instituted to cure or at least improve the disease. This model often fails to take two critical elements into account: the nonphysical needs of the patient and family and the fact that the vast majority of medical diseases in the twenty-first century are chronic, often progressive diseases that ultimately cannot be cured, only palliated.

In the medical model, the primary mode of communication between health care providers is often the written chart note, with the involvement of other medical specialists, as well as other professional disciplines. This system is often haphazard and uncoordinated.

The interdisciplinary/palliative care model is team driven, with the focus of care being the patient and family rather than the disease (10,11). Interdisciplinary care recognizes that the discipline that often spends the greatest amount of time with a patient and family is usually the nurse and the nurse is also equipped with the *broadest* assessment skills. The nursing assessment in palliative care, whether performed on a unit or in an ambulatory or community setting, is of paramount importance.

The nurse coordinates the plan of care for the patient and family as well as the interdisciplinary team, which can include physicians, social workers, and pastoral caregivers, among others (12). The nurse should have excellent physical assessment skills and a strong knowledge of current innovations in pain and symptom management as well as astute psychological and spiritual evaluation strategies to ensure the plan of care is congruent with the goals of the patient and family. The nurse is often in a position to develop the strongest therapeutic relationship with the patient and family.

The nurse works with the patient and family using skilled compassion and concern, empowering the patient to exercise control in decision making where possible, which can only enhance the patient's sense of control. The nurse continually reassesses patient and family goals, treatment preferences, coping abilities, and support needs. The nurse is the conduit for information and critical assessments, as well as evaluation of the patient and family goals within the interdisciplinary team. The physician can provide expertise about the disease, treatment options, risks and benefits, likely outcomes, and symptom management interventions. In addition, they can help to anticipate critical decisions and guide and support the patient and family through the process. In order to assess patient and family coping and identify individual strengths and community resources, a social worker is essential to the team. In addition, they are also most adept at evaluating and negotiating financial and insurance resources. Pastoral caregivers can be invaluable in helping to understand the patient's spiritual strengths and concerns and assist the patient and family in maintaining/reframing hope and establish meaning in the setting of advanced disease.

A key element of interdisciplinary palliative care is a strong emphasis on *coordination* of care. This is most commonly achieved through team meetings, where different disciplines verbally communicate each of their assessments in order to synthesize a comprehensive care plan that will meet the patient and family needs. For an interdisciplinary team to be most effective, candid communication between team members is vital.

The distinction between interdisciplinary and multidisciplinary practice is critical. In the traditional multidisciplinary team, care of the patient is directed by the physician (Fig. 46-1). Many other members of the health care team may be involved in the delivery of care, however, efforts are often uncoordinated and fragmented.

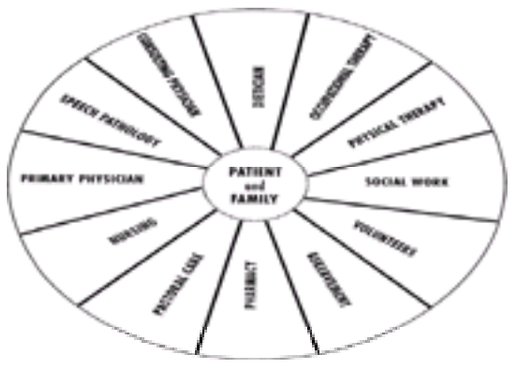

FIGURE 46-1. Multidisciplinary team. [From Krammer LM, Muir JC, Gooding-Keller N, et al. Palliative care and oncology opportunities for oncology nursing. Oncol Nurs Updates 1999;3(6):1–12, with permission.]

The primary mode of communication between disciplines is the medical chart. The result is often ineffective communication between professions, lack of accountability, and a tendency for each discipline to independently develop their own patient care goals. To contrast, in an interdisciplinary model, leadership is shared and communication between team members is collaborative (13).

Although individual health care providers may have discipline-specific goals as part of the plan of care, it is key that the team remains focused on the patient-driven goals. Communication between team members will be more effective if the focus of team interaction remains on the patient and family. Maintaining this focus is more successful when the team allows time to discuss the challenges individual professionals are facing in association with the patient and family and if the team regularly reviews the plan of care. This model allows for team members to *directly* interact with the patient and family and to provide consultation with each another in order to achieve the goals identified by the patient and family (Fig. 46-2). Thus, the sum (from the patient's point of view) is greater than the individual parts.

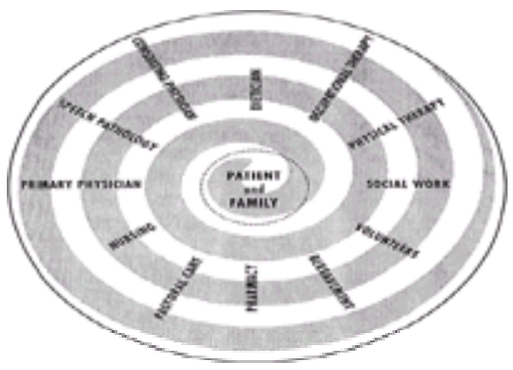

FIGURE 46-2. Interdisciplinary team. [From Krammer LM, Muir JC, Gooding-Keller N, et al. Palliative care and oncology opportunities for oncology nursing. Oncol Nurs Updates 1999;3(6):1–12, with permission.]

An effective interdisciplinary team mandates collaboration, decision making, leadership, and conflict resolution. *Collaboration* is defined as the ability to work jointly with others, especially in an intellectual endeavor. It is the process of collaboration that empowers team members to act as decision makers within the group. For example, if a question on pain management arises, various members of the team will provide observations and opinions from their professional perspective. The resulting plan of care will have a broader intellectual base, a multidimensional assessment of the patient's pain will have been performed, and interventions will be developed in an effort to maximize the relief of all components of the patient's experience of pain.

Using a true collaborative process, the decision maker would not determine a treatment plan based on his or her own perspective, rather the decision would reflect the team's input. Through this type of collaboration, effective patient-driven quality outcomes can be achieved. Good leadership provides a safe environment for an individual team member to lead in changing or adding to a plan of care, and a cohesive and supportive team is developed. As examples, the doctor who is able to step aside and glean insight into the patient's coping from the social worker or the nurse who knows when to consult the chaplain, illustrates collaborative practice by all four of these very different disciplines. Strong leadership is imperative to facilitate the peak professional growth of each team member and ensure that the focus of care is always directed toward the patient and family (10).

Due to the interdependency among team members, conflict inevitably arises. Conflict can be both beneficial and can challenge effective interdisciplinary team functioning. Lack of conflict may stifle creativity and professional growth. The challenge is not to avoid conflict but to manage it effectively so that patients, families, and team members can reap its benefits (14). Respect and trust in each member's skills, knowledge, and expertise are essential. Different ideas and opinions often stimulate innovative solutions for patient care problems. However, conflict can be destructive when it becomes personalized or is viewed as threatening to a team member's role.

Within a team there is often overlap of assessment and management skills. A nurse may be highly skilled at symptom assessment and be able to develop a full management plan. A physician may identify that the patient and family rely heavily on their faith as a source of strength in coping. Furthermore, the social worker may help to recognize that a patient's nausea is only brought on by discussion about leaving the hospital. In the following section, the components of the multidisciplinary assessment will be discussed. Which discipline is involved in assessing each of these areas will be different in each setting based not only on the individual team members but also on the unique needs of each patient and family.

COMPONENTS OF A MULTIDIMENSIONAL PATIENT ASSESSMENT

History of Illness and Treatment Responses

The initial elements of the MDPA parallel that of the traditional medical model. The assessment begins with an illness history that begins with determination of the primary diagnosis and course of treatment. In addition, attention should be paid to assessing the therapies that have been utilized, not only their impact on the disease but also their impact on the patient's symptoms from the disease and what therapies have exacerbated or ameliorated these symptoms. One must also elicit information about other illnesses and therapies that the patient has that may be important contributors to suffering and complicate subsequent therapies. One should have information on the extent/stage of disease, and familiarity with the diagnostic testing that confirmed the extent of disease.

Physical Assessment

The physical assessment is designed to screen for the presence of physical symptoms contributing to suffering. To ascertain the “subjective” symptom burden, one must inquire as to their presence and severity. Specific assessment tools can assist in the screening for multiple symptoms (15,16,17 and 18). The Edmonton Symptom Assessment Tool (15) is a concise, user-friendly, palliative care assessment tool (Fig. 46-3). Use of these tools may be helpful in building a therapeutic relationship by reminding patients that relief of their suffering is important to the caregivers. The physical assessment also includes understanding how symptoms impair function, sleep, movement, eating, mood, etc. In addition to the physical assessment completed by both the nurse and physician, there are a number of other disciplines whose input can be critical. Physical and occupational therapy assessments may reveal deficits and suggest interventions that can be essential to maintaining functional capacity, ensuring patient safety, conserving energy, and decreasing fatigue. A speech therapy assessment can provide valuable information regarding swallowing function, while a nutritional assessment by a dietitian can aid in determining caloric intake needs, thereby reducing cancer-related cachexia.

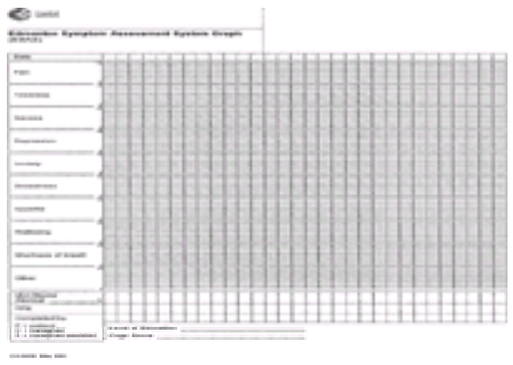

FIGURE 46-3. Edmonton Symptom Assessment Scale. (Reprinted with permission from http://www.palliative.org/PC/ClinicalInfo/AssessmentTools/ESAS.pdf.)

It is important to emphasize that most symptoms have physical, emotional, spiritual, and functional components. For example, dyspnea can be due to airway impingement by tumor, coupled with an emotional fear of suffocating. This in turn leads to limits on activity, and the patient asks, “What have I done to deserve this?” Each symptom should be thoroughly assessed to determine both the physiological/pathological etiologies and the nonphysical components so as to guide appropriate therapies.

The assessment of cognitive function is particularly important and can be readily determined via the Folstein mini-mental state examination (19). It is important to determine whether a patient has either acute (e.g., delirium) or chronic cognitive deficits (e.g., dementia) that would impair decision-making capacity and/or safety. Some palliative care programs utilize a mini-mental status evaluation as part of routine clinical practice for all patients.

Decision-Making Capacity

The principle of autonomy (or self-determination) dictates that a person who possesses the ability to make his or her own decision should be allowed to do so (1). When facing advanced cancer, there are a number of critical decisions that individuals must make: decisions about whether or not to receive anticancer therapy treatment to what type of therapy, whether or not to enter a clinical trial, as well as advance care planning decisions (living wills, durable power of attorney for health care, resuscitation wishes, etc.). Potential crises can be avoided if advanced care planning decisions are discussed while the patient is fully cognizant.

When there are any questions about a patient's decisionmaking capacity, a full mental status examination should be completed. Every effort should be made to treat a reversible cause of altered mental status to return the patient to a state in which they possess decision-making capacity. It is important to be aware that only a court judge can determine someone as “competent” or “incompetent.” It is the health care provider's clinical determination of “decision-making capacity” that serves as a guide for sharing critical clinical information and obtaining informed consent (1).

Information Sharing

A key part of the MDPA is assessing the patient's wishes and desires for the sharing of information. While Western medical ethics emphasizes autonomy, truth telling, and informed consent, it is important to recognize that not all cultures and practices agree with this approach. Robert Buckman, MD, has written a helpful six-step protocol for communicating difficult information (20). In this method, one must remember to ask patients how much they know about their disease with an open-ended question such as, “What is your understanding of your disease?” followed by active listening. This should be followed with a second, perhaps more important question that is again open-ended: “How much do you want to know about your disease?” followed by active listening. When one is still not certain about how to proceed in the sharing of information, a follow-up question that is useful is, “If I have some important information to share about your medical condition, with whom would you want me to share it?”

Psychological Assessment

A psychological assessment should be done to evaluate mood and coping. It is important for team members to develop a sense of familiarity with each of these areas and, most important, to recognize when there are issues that need further assessment and/or intervention by another health care discipline. Most palliative care and hospice teams rely heavily on social workers and nurses to provide expertise in detailed assessments of mood and coping. When the initial assessment suggests significant needs, then referral to a mental health provider can be helpful. Social workers generally have a well-developed network of mental health providers in the community that can be called on for counseling (individual, group, couples), support groups, and, potentially, pharmacological therapy.

The assessment of mood is vital in the palliative and supportive oncology arena (21). Anxiety and depression are common among cancer patients. Depression is common in advanced cancer and often undiagnosed and untreated (21,22). Many clinicians believe that it is “normal” to be depressed when one has advanced cancer. Although it is true that mood disorders are common in advanced cancer, depression is not normal and warrants pharmacological and nonpharmacological therapy. Involvement of a mental health provider to provide further assessment and intervention may be beneficial. The health care provider must always be alert to the possibility of significant depression leading to suicidal ideation (23). If this is suspected, one must make an immediate assessment of whether or not the patient has a plan to act on this idea and whether they will “contract for safety” (let someone know if they feel that they might act on their plan). In any case, the presence of suicidal ideation requires prompt intervention.

The diagnosis of advanced cancer is often devastating to a patient and the family (24). There are a number of responses that a person can have to this threat to his or her personhood, including fear, anger, avoidance, denial, intellectualization, intense grieving, and existential questioning. All of these coping mechanisms are normal and may be adaptive and beneficial to the patient and family at that particular time. It is imperative that the health care provider continually assesses the emotional coping of patients and families to determine when there may be problematic coping. It is helpful to assess not only current coping strategies used by the patient and family but also strategies used in the past. This will assist the team to anticipate ineffective coping styles and to develop individualized strategies for the patient and family members. General open-ended questions (e.g., “people often feel a number of different emotions as they are living with cancer, what are you feeling?”) followed by active listening can be very helpful. With good psychosocial support from the cancer care team, most patients can effectively live with their cancer as they reach acceptance and, ideally, peace with their illness and their life.

Social Assessment

In the MDPA it is important to keep in mind that the patient and family, rather than the disease, are the primary focus of care. One needs to glean a basic understanding of the patient's family and family dynamics, their culture and community, and relevant information about their finances. The social worker, often in conjunction with the nurse, can help to obtain critical social information.

Each patient and family will experience illness within the context of their particular worldview. Being sick, even slightly, can be a disabling experience, both physically and psychologically, with attendant feelings of loss of control and helplessness becoming paramount. This is particularly so in terminal illness. For example, the change of role within the family can become a critical issue. Perhaps the patient who is the primary income generator is unable to work and thus unable to provide materially or the main family caregiver is too ill to continue lifelong habits of looking after other family members. For the entire family there often needs to be major adjustments made. Financial, social, and emotional adaptations will occur with varying effectiveness. In order to open communication and provide whole person care, the patient and family must be integral members of the team and thus involved in treatment decisions and in development of an appropriate care plan (25).

A patient's entire family system is affected by the diagnosis of a life-threatening illness (26,27). The patient's relationship to his or her world changes with the news that his or her life span has been defined, thus altering their family interactions (28). The patient's roles within the family—as a provider, a caregiver, a parent, a spouse, or a sexual partner—may be challenged (26,28). Therefore the particular issues and needs of family members, in addition to the patient, must also be assessed. Furthermore because care may be provided by family members in the home setting, the family should also be consulted and educated about the diagnosis, treatment options, the illness trajectory, symptom burden/treatment, and care giving—with the patient's permission (28).

What constitutes “family” will vary for patients. It is vital to determine whom the patient considers to be his or her “family” or “community of care,” whom they wish to be included in decision making, and whom he or she identifies as his or her means of support. Family units can be composed of the traditional nuclear and extended family, but also may be a same-sex couple, members of a religious order, members of an ethnic/cultural community, or simply a group of friends. Focused discussion with the patient should occur up front to determine whom they identify as “family,” with whom they wish to share information, and how much and what type of detail they

wish to share.

Social workers use the genogram or family tree to facilitate understanding of a particular family's structure and dynamics. The genogram helps to identify the family structure in a clear and comprehensive way. It highlights relationships, strengths, and weaknesses and can often clarify some of the family norms around disease/illness and coping. Gathering the information to develop a genogram also facilitates the partnership between the health care team and the patient and family. The information gleaned should be documented in the medical record and reassessed periodically.

As discussed earlier (see the section Decision-Making Capacity), the importance of addressing advance care planning for the patient and family is critical (29) and is best addressed early in the course of illness, and frequently reassessed, rather than left for discussion at 3 a.m. in the emergency room when a crisis occurs. Early discussions regarding prognosis, likely course of the disease, events to anticipate, and clarifying advance directives (e.g., living wills and/or designation of a durable power of attorney for health care) all can serve to mitigate subsequent dilemmas, increase control, and lessen angst. This helps the patient and his or her family to prepare for changes in the patient's condition and facilitates open communication between the patient, family, and the health care team (26). This type of communication minimizes the sense of abandonment that many patients fear and helps facilitate a sense of control (27,30).

It is important to determine specific cultural or other particular practices of the patient and family in order to be sensitive and respectful. If the health care provider encounters an unfamiliar culture, custom, or tradition, he or she should use this as an opportunity to learn about it from the patient and family or from a local expert. This will not only enhance the health care provider's knowledge base and skill set but also show significant respect for the patient and family that will help to build a therapeutic relationship (31). The social worker or chaplain is often an initial resource for these issues.

A critical component of the social assessment is to determine patients' financial issues or concerns. Medications are expensive and often are not covered by insurance, resulting in either significant out-of-pocket expenses for the patient or lack of adherence to a medication regimen. Finally, one should always be aware of the burden that many patients and families feel as they are going through their illness. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT) study found that 31% of all families spent most or all of their savings on the treatment of their terminal illness, with 29% reporting loss of the major source of income (32). Both nurses and, in particular, social workers can be extraordinarily helpful in determining the family resources and potential concerns.

Spiritual Assessment

A spiritual assessment can provide another link to a better understanding of a patient's suffering (33). A pastoral care provider is an invaluable member of a team in this regard. The fundamental component of the spiritual assessment is to listen to patients to determine the meaning of the illness to them. This may or may not have anything to do with formal religion, but may reflect more of a struggle over patients' own issues of “ultimate concern”; fears about the future for both themselves and their loved ones; desire to not be a burden to their family members; issues of losses of control, independence, hope, and their changing role within their family, community, or workplace; fears about their own death; and the questions around dying.

Many of these concerns, if not assessed and addressed, grow and can lead to spiritual crisis where feelings of guilt, unworthiness, hopelessness, and abandonment fulminate. One must listen and then ask open-ended questions like, “How have you tried to make sense of what's happening to you?” or, “What are some of the things that give you a sense of hope?” (2), and then be prepared to listen to the response to understand the patient's sense of meaning.

If the patient and/or family have a particular faith tradition, it is important to emphasize that a religious leader or the faith community may be a useful source of strength (34). A skillful pastoral care provider can be extremely effective in addressing spiritual angst, even when the patient and family do not identify with a particular religious or spiritual doctrine.

Practical Assessment

The final area of assessment is the practical assessment (35). Issues to consider here are whether or not the patient will need help at home in the form of a formal caregiver. If so, how many caregivers will be needed to ensure safety and good care, and what are the possible care options given the patient and families' financial resources. The assessment should include a determination of the patient and family needs in terms of activities of daily living. For example, shopping for food and food preparation; bathing, dressing, and hygiene; and transportation issues, such as determining how the patient will get back and forth to the clinic, are all issues that, although they are often perceived as “nonmedical,” often have an impact on the ability to deliver appropriate medical care. Planning for likely changes in patient function can help to reduce the chance of a crisis developing. Nurses are particularly skilled at anticipating the practical problems that may befall the person with advanced disease.

Prior to the patient becoming bed-bound, the need for equipment, such as a hospital bed, bedside commode, or shower chair, should be discussed. Before the patient loses the ability to swallow, issues of nutrition and medication administration should be explored with the patient and family, so that an anticipated plan can be put in place.

SUMMARY AND CONCLUSIONS

As medical technologies and therapies have converted many illnesses into chronic conditions that people have to live with for months or perhaps years, it is important to remember that medical illness affects every aspect of individual and family life. In the setting of palliative and supportive oncology, there are a number of domains of whole patient assessment that should be obtained on the initial visit that are perhaps different from those currently obtained in the traditional medical model. Although these additional domains of assessment may seem overwhelming both in time and emotion for one clinician, it is what our patients and their families are expecting. Thus, it is imperative that our training in oncology nursing, social work, and medicine (surgical, radiation, and medical oncology) has the principles of Primary Palliative Care that are embodied in the MDPA as core competencies in clinical practice (2).

Furthermore, medical professionals, regardless of their own discipline-specific training, must learn to more fully respect and collaborate with colleagues in other disciplines, to integrate their assessments, share the burden of the issues that will be revealed, and ultimately achieve better outcomes for patients and families in terms of whole person care. Ultimately, through this effort, the health care provider will also find, as others have documented, that, through interdisciplinary teamwork, “the sum is greater than the individual parts,” leading to greater personal and professional satisfaction for all clinicians involved in palliative and supportive oncology.

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47

CROSS-CULTURAL ISSUES

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People experience both health and illness in cultural contexts. A better understanding of culture helps the clinician avoid certain pitfalls, thereby improving the chances of good outcomes. Very sick and dying patients in our society are often dependent upon care from people of very different cultural backgrounds, making misunderstanding and conflict common. Culture, as a topic area, is almost infinitely broad. A comprehensive discussion of culture and palliative care would require considerations from anthropologic, sociologic, historical, and philosophic perspectives, among others. Such a discussion is beyond the scope of this chapter, although I will draw on some perspectives from beyond standard medical texts and journals.

Various definitions of culture exist in the literature. Helman defines culture as “a set of guidelines (both explicit and implicit) which individuals inherit as members of a particular society, and which tells them how to view the world, how to experience it emotionally, and how to *behave* in it in relation to other people, to supernatural forces or gods, and to the natural environment” (1). This definition suggests culture, as a noun, exists as a pervasive set of guidelines shaping the individual. Of course the existence of any such guidelines and associated patterns of behavior and organization results from the actions of many people. The ongoing construction, shaping, and reshaping of culture demonstrates that culture, as a *verb*, is in fact more than an inheritance; it is a dynamic *process* wherein people interact with each other and thereby actively create an ever-changing world experience. Another way to view culture is as a complex and overlapping set of descriptors, adjectives, and adverbs, giving meaning, shading, and even texture to various patterns of human organization and behavior.

The following discussion proceeds on the assumption that clinicians, patients and their families share a common goal—an optimal outcome relative to a particular episode of illness or clinical encounter. Unfortunately, consensus is often lacking as to what might constitute an optimal outcome and what action(s) may give rise to such an outcome. While any group of people share some common aspects of human experience (e.g., at a minimum all people struggle with similar human bodies), individuals and groups may participate in and view the world in terms of health and illness in radically different ways (2,3). We are for the most part unaware of the degree to which our views differ from others. As Hall put it, “culture hides much more than it reveals, and strangely enough what it hides, it hides most effectively from its own participants” (4). It is often only when we encounter others in conflict that we begin to become aware of alternative viewpoints. In such encounters there is an understandable, but regrettable tendency to affirm one's own view through reinterpretation of the other's viewpoint according to one's own position or, where this fails, by dismissing the other's perspective as incorrect, nonsensical, or bad (5,6). The inherent difficulty of transcending one's own viewpoint is a significant barrier to collaborative efforts to obtain optimal outcomes for both clinicians and patients. However, those involved have little choice but to struggle in the direction of understanding and collaboration. Barring this, disagreements will undoubtedly be resolved by explicit or implicit force (7). Better communication and mutual understanding will not resolve all disagreements arising in crosscultural encounters. However, the probability of achieving good outcomes will be significantly increased by efforts to understand the other and in turn to be understood.

Outcomes of care are also strongly affected by social forces and institutions that encourage certain courses of action and limit others, with profound effects both good and bad (8). Although clinicians may like to believe that their skillful therapies are the most important factors in achieving good health outcomes, other forces outside of their direct control may in fact be equally critical. For example, Morrison found that a ratelimiting step in getting patients needed opioids in innercity New York was the availability (or rather lack thereof) of such medications in neighborhood pharmacies (9). Pharmacies in nonwhite neighborhoods were significantly less likely to have adequate opioids for the treatment of severe pain than pharmacies in predominantly white neighborhoods. Getting pain relief to the patient was as dependent upon complex historical and socioeconomic factors giving rise to poverty and crime as it was on physician prescribing practices.

Clinicians would do well to consider the social forces affecting care and outcomes. Although most forces will admittedly be beyond the clinician's direct control, knowledge of both the opportunities and barriers such forces offer may enable the clinician to “work the system” for the good of the patient. For example, in attempting to support a frail patient trying to receive medical care at home alone, the clinician must wrestle with various societal forces that “created” a situation in which frail patients find themselves alone at home and a health care and social support system that is poorly equipped to provide such care. Rather than give up altogether, the clinician needs to become familiar with how to access what support *is* available. How does one recruit community support from various organizations that may view the patient as “one of their own”? Support may be found from groups organized around such cultural attributes as ethnicity, age, disability or disease, gender or sexual orientation, among others. Engaging such support, although not traditionally considered medicine, may in fact be “just what the doctor ordered.”

IMPORTANCE OF CULTURE TO PALLIATIVE CARE

We live in an increasingly pluralistic society. Although American culture as we now conceive of it evolved out of a history of European immigrant subjugation of Native Americans, waves of immigration from other societies have contributed to making the United States a culturally diverse nation. The extent of such ethnic diversity varies dramatically by geographic region. Pluralism exists not only in terms of ethnicity but other cultural attributes. National or geographic origin, current home (geographic, urban/rural), gender, sexual orientation, marital status, family, professional and community roles, religion, economic and educational status—these cultural attributes and others contribute to our cultural personae. Certain cultural attributes become defining to the extent they can be considered subcultures in their own right. For example, we now name generations (Baby Boomers, Generation X). Some subcultures are now large enough that individuals and families can live within them with limited, often superficial exposure to people from other subcultures.

Pluralism exists also among health care workers (10). When people become ill, particularly chronically ill, they are more likely to come under the care of others from very different backgrounds than their own (5). Relationships in such situations are often imposed. That is, health care workers, whether physicians working in an intensive care unit or nurse's aides in a nursing home, and patients have limited choices as to who will care for whom. Because handson care, such as that provided by nurse's aides, is devalued in our society, immigrant and underclass workers make up a substantial portion of this workforce. These workers have little choice but to accept positions at the bottom of the social ladder, which in our society includes the provision of the most intimate care for chronically ill and dying patients. Conversely, patients and families are increasingly dependent upon care provided by such workers. It should come as no surprise that imposed relationships at such a fragile stage in the life cycle create a problematic environment. Efforts to understand each other are not only desirable, they are essential if there is any hope of obtaining reasonable outcomes.

Although culture lurks in the background of all human experience, it comes alive and overt during transition periods in the human life cycle. In such dramatic transitions as birth, coming of age, marriage, and more recently retirement, culture provides mechanisms to make human what would otherwise be mere biology—birth, puberty, mating, and aging. Dying is obviously a major life transition and as such is heavily invested with culture. However, more subtle transitions usually precede actual death. Consider, for a moment, cancer as an example. Becoming a “cancer patient” implies a transition to a new category of being. The newly diagnosed cancer patient may transition to states of “survivorship” or cure, remission, or terminality—all with profound implications for how the person is understood by self and others to exist within the broader context of society (11).

Cultural transitions are often marked by ritual and rites wherein meaning is expressed and created through particular behaviors. Beyond this, ritual is used to change reality or at least to create a particular human expression of reality. For example, in a comingof-age ritual one *becomes* a man or a woman, making *human* the more biological process of puberty. Rites and rituals related to palliative care are most obvious in considering death and dying practices such as funerary rites (12,13,14 and 15). More subtle may be myriad behaviors, some of a very personal nature, that are used to engage with the multiple transitions involved in becoming chronically ill. Ritual is involved in the process of making a person a patient in a hospital. Wristbands and hospital gowns serve ritual purposes beyond mere technical efficiency. The ritual use of wigs or caps after hair loss through chemotherapy is another example that may serve the purpose of maintaining a certain image of self (in addition to keeping one's head warm). Conversely, “going bald” after hair loss may serve a ritual purpose of declaring acceptance as a new member of a class of cancer patients.

The importance of ritual as a cultural activity related to dying (and birth) is highlighted by Grimes in his book, *Deeply into the Bone— Reinventing Rites of Passage*.

> If we do not birth and die ritually, we will do so technologically, inscribing technocratic values in our very bones. Technology without ritual (or worse, technology *as* ritual) easily degenerates into knowledge without respect. And knowledge without respect is a formula for planetary annihilation. It matters greatly not only *that* we birth and die but *how* we birth and die (13, p13).

Serious illness and dying as life transitions also challenge how individuals construct their life stories. Gaining a better understanding of such stories, often entitled *illness narratives*, as discussed later in this chapter (see the section Explanatory Models and Illness Narratives), is critical to good palliative care (16,17,18,19,20 and 21). Such narratives give some insight into the personhood of the patient. Palliative care and supportive oncology differ radically from traditional biomedicine in taking the *personhood* of the patient in all its multifaceted dimensions as the focus of care. Such personhood cannot be seriously considered separate from its cultural context, which both shapes and is shaped by that personhood.

CULTURAL EDUCATION AND PALLIATIVE CARE

Biomedical curricula rarely include cultural aspects of care in their content, despite studies calling for such inclusion (22,23,24,25 and 26). A study in 1992 queried 126 medical schools regarding possible courses in “cultural sensitivity.” Of 98 respondents only 13 schools reported offering such courses and all but one were elective. Fifty-nine schools indicated that they had incorporated cultural sensitivity in other courses such as courses on medical ethics (27). A systematic review of the literature from 1963–1998 published in 1999 found 17 reports of curricula meeting search criteria (28). Thirteen of these programs were in North America and 11 were exclusively for students in year 1 and 2 of medical school. The focus of most of the content was on ethnicity, attitudes, health beliefs, and language barriers. Only one program is reported to have considered anthropological and sociological theories (29). The lack of breadth and apparent lack of depth of training suggested in this review is discouraging. However, there are some encouraging signs of change. Recently, Carrillo and colleagues published a description of a course for medical students and residents consisting of four 2-hour modules covering *basic concepts core cultural issues, understanding the meaning of the illness, determining the patient's social context, and negotiating across cultures,* which seems to be more in keeping with recent anthropologic and sociologic trends (30). In an intervention designed to assist internal medicine programs in the United States in improving palliative care education, Weissman found that teaching regarding cross-cultural issues was high on the list of unmet needs of residency training programs (31). In response to this, a module on addressing cross-cultural concerns was developed for that intervention and incorporated into the curriculum (32). This suggests that physicians are experiencing some tension regarding their lack of training in cultural issues, which bodes well for future educational efforts.

ETHNICITY

What little clinician training that has occurred regarding culture has focused heavily on ethnicity, as have palliative care texts and articles (33,34,35,36,37,38,39,40 and 41). The tendency in most such texts is to describe beliefs and practices of particular ethnic groups relative to health care. Lipson, for example, provides overviews of how 24 ethnic groups construct illness, relate to symptoms such as pain, decision making, relations with clinicians, preparations for dying, grief practices, and death rites, among others (34). Although this and similar texts may be helpful to clinicians struggling to care for patients from very foreign ethnic groups, some caution is in order. Excessive reliance on such texts risks stereotyping by underestimating the extent of cultural diversity within ethnic groups (42,43). Culture tends to be portrayed more as a determinant *thing* separate from personhood, like the genetic code, rather than an active *process* of social engagement. An exclusive focus on ethnicity and associated “beliefs and practices” also tends to narrowly define culture and limits the ability to appreciate other important aspects of culture (6, pp1–24, 10). For example, problematic, cross-cultural encounters between individuals and health care systems may too easily be ascribed to differences in belief systems, with inadequate attention to social forces associated with ethnicity such as arise from poverty or racism. A cursory or narrow read of such texts (far narrower than intended by the authors) might leave the reader imagining culture as an “inconvenient barrier to a rational, scientifically based, health care system, a feature of ethnic “others,” as Koenig put it, rather than as dynamic process of social engagement in which clinicians participate every bit as much as patients and their families (10).

Ethnicity is a useful starting point for considering the myriad social forces that affect care and associated outcomes, as long as one understands that considerably more than “beliefs and practices” associated with ethnicity are at work. Correlated with ethnicity are such important factors as immigrant status, educational background, socioeconomic status, geographic and demographic distribution relative to health care resources, communication styles, gender, and other social roles (44,45,46,47,48,49 and 50). Space does not allow a detailed discussion of all these factors, although they undeniably affect clinician interactions with patients and families, and outcomes in profound ways.

CULTURE OF BIOMEDICINE

Let us consider biomedicine as a culture, particularly as it has evolved in the United States. Originating in Western Europe, the evolution of biomedicine has been guided by complex historical, religious, philosophical, and economic forces (8,51,52). Biomedicine has now become, arguably, the dominant medical system throughout the world, being integrated or at least coexisting with numerous other medical systems. This term, now preferred by most anthropologists, may be new to many clinicians. As Kleinman states, “If you ask biomedical professionals what word they would use to describe their field, most will say, in a powerfully succinct usage that does capture a sense of the hegemonic selfperception that has become almost a caricature worldwide, 'Why not just call it medicine?'” (3, p25). Insight into cultural aspects of biomedicine is critical for the practitioner trying to work with individuals across culture. This is especially true for those working in palliative care, which exists “at the margin” of biomedicine. Some might argue that as biomedicine depends upon scientific inquiry and rationality it has somehow risen above the messiness of culture. Any such statement would only reflect an arrogance common to the culture of biomedicine, highlighting a restricted world view. Biomedicine has undeniably resulted in astonishing and useful therapies, but it is *not* culture free. Biomedicine is not a monolith and in such a brief inquiry, stereotyping is a serious risk (53). Still, what characteristics and tensions can we identify within the world of biomedicine?

While sharing with other medical systems a fundamental charge to heal the sick, the emphasis in recent decades has been increasingly to fix broken bodies (18,52). Citing *Stedman's* definition of “medicine” as a profession, “the art of preventing or curing disease; the science that treats disease in all its relations,” Hahn points out that, “A prominent feature of Stedman's definition of the domain of medicine is the designated subject of medical work: medicine prevents and cures, studies and treats, not persons, nor their bodies, but the disease of bodies. In describing the domain of medicine, there is no mention of persons” (18, p133). Pursuing a Western rationalist belief that the *good* is best approached through scientific inquiry, biomedicine has developed a *mechanistic* approach to care. Through a progressively refined and reductionist understanding of the origins of illness, labeled *disease*, the hope (and the myth) is to eliminate physical disease entirely. As an important corollary, suffering will magically vanish once the physical disease from which it originates is eliminated and proper functioning restored. Although suffering is not entirely ignored in biomedicine, it does take second place to biology as an issue of concern. The belief that suffering is entirely derivative to biological malfunctioning is naïve on two fronts. First, it simply takes no account of aspects of suffering not arising from the body (54,55,56 and 57). As evidenced throughout this book, suffering is far more complex than this. Second, almost too obviously, biomedicine to date has failed to eliminate disease. Given our continuing mortality, inevitably the elimination of one illness must, by default, increase the probability of becoming ill and eventually dying from something else. As Fabrega writes, “The curing of disease, the technical repair of the machinery of the body, and the illusion that most, if not all, diseases can be undone, cured, or eradicated are guiding imperatives rather than a sensitive appreciation of the inevitability of sickness and a furtherance of caring for the suffering it entails” (52, p299). Suffering continues. Indeed, biomedicine “creates” new forms of illness and associated suffering, as the field of supportive oncology, dealing in large part with the sequelae of oncologic treatment, is ample testimony (58). The evolution of palliative and supportive care, pain clinics, and hospices as social phenomena on the margin of biomedicine can be understood in part as reactions to the failure of this dominant myth of biomedicine (Table 47-1).

Individualism	⟷	Reductionism
Autonomy		Paternalism
Disease in the individual body		Mechanistic/technologic approach to illness
Consumerism		Bureaucratization
Egalitarianism	⟷	Capitalism
Health care as a right		Health care as commodity

Lacking in modern biomedicine
- Focus on suffering as primary object of medicine
- Inclusion of a concept of a life force in model
- Illness as something transcending the individual

TABLE 47-1. TENSIONS IN THE CULTURE OF BIOMEDICINE

Individualism and egalitarianism, so central to our society, have also affected the culture of biomedicine. Biomedicine defines disease as something that resides within

the individual body (3). Such a narrow focus tends to ignore societal forces that broadly impact health. For example, we tend to focus on deranged cells in a particular patient's lungs to identify a disease we call lung cancer rather than identify a complex societal illness related to tobacco production and use, involving corporations, governments, tobacco farmers, and the resultant devastation affecting whole groups of people. Individualism also gives rise to the dominance of autonomy as a principle of bioethics and the recent tendency toward consumerism in medicine (59,60 and 61). Countercurrents to individualism also exist, resulting in considerable tension. Curiously, the emphasis on *disease* in the individual body as the proper object of concern itself negates the personhood of the individual (3, pp21–40). The high-tech, high-cost, big-business nature of modern biomedicine defines health as a commodity, rather than an aspect of personhood, to be purchased by consumers. Tensions inevitably arise from the simple fact that both the consumers of health care and of the commodities marketed by health care as an industry are the same people. Reports in the lay and professional press too numerous to cite speak of the dehumanizing nature of modern biomedicine as experienced by patients, and increasingly, practitioners.

Egalitarianism has been a philosophic underpinning of our democracy. Egalitarianism in health care tends to play out in terms of an evolving belief in a *right* to health care. In the early 1960s this notion gave rise to Medicare and Medicaid as institutions to provide care to elders, the disabled, and the poor as special classes of citizens deserving protection. Recently, a rights-based advocacy has arisen relative to palliative and end-of-life care. A “right to die” has also been advocated. The Supreme Court cases, *Washington vs Glickman* and *Vaco vs Quill*, revolved heavily around whether such a right exists (62,63). A strong countercurrent to such egalitarianism is a capitalist tradition in the United States regarding biomedicine as an *industry*, like others, to be affected by market forces and guided by an elite class of professionals, physicians. It is noteworthy that the American Medical Association, as spokespersons for this industry, strongly opposed both Medicare and Medicaid when first proposed in the 1960s as threats to private enterprise and “the American Way” (8, p126, 51, pp367–370). How else are we to understand the fact that the United States is the only Western industrialized nation without some form of nationalized health care, other than as a manifestation of industrialized medicine, strongly influenced by a spirit of rugged individualism?

Kleinman also points out that that biomedicine is unusual in its inattention to any concept of a “life force” (3, p36). Most other medical systems include some notion of a life force and commonly frame the understanding of health and illness in terms of balance and imbalance between aspects of energy (often positive and negative) that give rise to a life force (6, pp101–110). Examples include Chinese (yin-yang) and Mexican (hot-cold), among others (64). A medicine that identifies healing as a process of *balancing* seems philosophically closer to the spirit of palliative care than a medicine based on *cure*. Palliative medicine could benefit from a deeper understanding of such medical systems.

Biomedical culture influences care not only at a macro level, but also at more intimate levels. Good, for example, writes of the complex process of acculturation by which people become physicians in the world of biomedicine through multiple acts of engagement with a world rather foreign from lay life. A quoted medical student states,

> It often seems like as medical students we kind of slide into doing these kind of things which can have just unimaginably great consequences for patients and we just sort of do it because we've incrementally learned about the biology and the science and the pathology and the pharmacology and we kind of inch into it and suddenly there we are saying, “I'll write the orders that such and such be done to this patient” (65, p81).

Our cultural personae as clinicians are shaped to a large degree by innumerable small interactions with teachers, colleagues, and our patients. Attention to such details of everyday life in biomedicine is as important as attention to macro forces and belief systems and is particularly important for those in palliative care trying to change biomedical culture. Educational efforts that do not appreciate and work with the details of everyday clinical life will ultimately fail.

Palliative medicine and supportive care working at the margin of biomedicine constitute a radical challenge to many of biomedicine's tenets. The emphasis on the person and family as the unit of care and the attention paid to suffering highlight the nature of this challenge. It should come as little surprise that resistance to such change has been engendered on the part of many in biomedicine.

BIOETHICS

When cross-cultural and other conflicts arise in biomedicine, at least those conflicts identified as such by clinicians, the tendency is to try and resolve these conflicts through bioethics, as codified in law, accrediting agency, and local policies, and through ethics consultations. Leaving aside whether all such conflicts are in fact conflicts of ethics, this is a cultural phenomenon worthy of consideration. Bioethics, as a process of dispute resolution, seeks good outcomes through a weighing of ethical principles as understood to be manifest in a particular case (66). Modern bioethics also attempts to balance viewpoints—those of patients and families as well as clinicians—in seeking resolution. As such, bioethics can be a vehicle for the promotion of mutual understanding—clearly a good thing. However, without reflection upon cultural biases giving rise to bioethics, the discipline risks becoming an agent of social control for the culture of biomedicine and thus risks squelching true mutual understanding.

Anthropologic critiques of bioethics are limited, but raise important issues of concern (67,68 and 69). Often noted as “ethnocentric” positions of bioethics are the following:

- The dominance of abstract ethical “principles” as prime movers for decision making, based on tenets of Western philosophy.

  Classically four such principles are identified—autonomy, beneficence, nonmaleficence, and justice (70). The process of using abstract principles as prime movers betrays a cultural bias. So too does the choice of specific principles. For example, *interdependence,* valued by so many non-Western cultures as a principle for decision making, might be included as a counterweight to autonomy (71).
- A tendency to make “practical” such abstractions through the practice of ethics consultations, especially in the United Sates.
- Codification of such abstractions in a plethora of laws, regulations, and policies, reflecting the bureaucratic and litigious tendencies of American society (72).
- The dominance of autonomy as a guiding principle (73,74).

  Spinning off from autonomy is an almost unassailable insistence on surrogate decision making and associated substituted judgment as the only proper vehicles for deciding a course of action relative to patients lacking capacity. The anthropologic basis for surrogate decision making is ighly questionable (75). The first U.S. legal case to invoke the principle of surrogate decision making (Quinlan) occurred in 1976. The term *substituted judgment* was first used in a 1980 Massachusetts case (in re Spring) suggesting the historical roots of this “belief system” are shallow (72, pp172–173). Even a cursory examination of decision making for incapacitated patients across world cultures would find very few examples of groups espousing surrogate decision making as a guiding value. One could argue that the primacy given to surrogate decision making reflects the limited view of a very small subculture of Western bioethicists (and the courts and policy makers who seem to share this view) (5).
- Suffering as a derivative, not a primary concern of ethics.

Kleinman suggests that bioethics could be improved by an infusion of “ethnographic work,” resulting in an inquiry grounded less in abstract principles and more in the cultural contexts of participants. He argues that such an approach may be a means of protecting patients from ethnocentric tendencies of biomedicine.

> As part of this ethnographic work, bioethicists need to elicit the perspectives of the participants and place them in the contexts of family, workplace, and medical system. To interpret these grounded perspectives, however, they will need to construe the local context in the light of larger societal influences. Thus, by bringing the life world of the patient into biomedical deliberations, bioethicists also bring with that biographical narrative a much larger societal analysis.
>
> The bioethicist's involvement should be to facilitate communication and to help negotiate conflicting orientations. In this work, it is necessary to protect the participants from the dehumanizing imposition of hegemonic principles like autonomy and justice (3, pp54–55).

Of note in this quotation is his inclusion of both “larger societal influences,” what I have termed social forces, and personal narrative as relevant to bioethics, and his suggestion that negotiation facilitated through better communication is more relevant that the pursuit of some abstract good (71).

EXAMPLE OF NONDISCLOSURE

Let us consider a request for nondisclosure as an example of a classical “ethical” dilemma, which may in fact be better addressed through ethnographic inquiry (76,77). The scene is well known to most clinicians. A relative requests that the clinician not inform a patient of some bad news such as a diagnosis of cancer or a terminal prognosis (78). Such a request appears to conflict with autonomy as a guiding principle and multiple health care policies that stress the importance of informed consent. The dilemma is doubly difficult because the request, usually from family members, that clinicians either not talk or frankly lie to the patient inhibits open communication that might resolve the issue.

A narrowly applied bioethics could do serious harm in such a case. Rigidly insisting that the patient has “the right to know” could both alienate family members and

damage the patient by forcing undesired information. Anecdotal case reports suggest that some patients, if bluntly told of their prognosis, will in fact lose the will to live, as families sometimes warn. Orona and Veatch both suggest a possible resolution to the problem based on a twist of logic, which recognizes that autonomy can be reframed as a choice *not* to act independently but to defer to others (73,79). The trick is how to identify such a choice on the part of the patient without giving undesired information. In practice, as Kleinman suggests, skill must be used in exploring the "local world" of the patient and the family and then negotiate, where possible.

Requests for nondisclosure seem more likely from individuals from *high-context* cultures (to be discussed further later [see the section Intercultural Communication]) (80,81). High-context cultures place more weight on the contextual and relational aspects of communication as compared to more linear, verbal communication typical of Western biomedicine. Charlton's review of nondisclosure cites articles demonstrating that Spaniards and Italians (both relatively high-context Southern European cultures) were more likely to not desire disclosure for themselves as compared to Australians (a relatively low-context culture) (76). Conflict resolution in high-context cultures is often more dependent upon the quality of the relationship between individuals than on the power of verbal argument. Thus, prior to tackling directly a problem such as a request for nondisclosure, the clinician is advised to try and understand both the patient and family context in which this request is being made and the relationship that is evolving between the family and the clinician/health care system. To the extent a strong, trusting relationship can be fostered, conflict resolution will proceed more smoothly. Conflict resolution in real situations is usually more dependent upon communication skills than an abstract understanding of dueling ethical principles. By way of example, let us consider what skills might be useful in addressing a request for nondisclosure.

COMMUNICATION SKILLS IN ADDRESSING NONDISCLOSURE

At the simplest level the clinician should state and demonstrate *respect* in the face of such a request (32). Recalling that family-based decision making and nondisclosure are common worldwide, and recognizing that courage is often needed to make such a request in the face of a powerful health care system that generally disapproves of nondisclosure, may help the clinician engender respect.

Exploration of the context may begin with the person(s) making the request for nondisclosure. Why are they making this request? How do they understand the roles of participants, both in the family and clinicians relative to care? What do they fear might happen if the person knew? What are their hopes?

Just as cultures are not monoliths, neither are families. It is quite possible for a family to believe the patient does not want to know when in fact he or she does. The clinician might then inquire how the family and specifically the patient have dealt with similar situations in the past. The clinician might ask questions such as, *"Do you think or know that she would agree with this? Have you discussed this approach with her? How has she dealt with similar situations in the past?"*

Exploration is not a one-way street; it is not the same as *taking* a history. Clinicians are advised to share their (often equally foreign) biomedical viewpoints and to share dilemmas being confronted, including policies that require informed consent. For example, beyond the mundane (getting consent forms signed), clinicians may share that they too wish only the best for the patient. One might say that in one's experience some people even in cultures that practice nondisclosure really want to know and that if this were so, nondisclosure might cause the patient distress and this would bother the clinician. The clinician might explain that he or she values truth telling and could not lie if asked directly a question. Hopefully finding the presumed common ground of wishing the best for the patient will foster some mutual understanding.

The clinician probably will want to explore the patient's understanding and concerns. The intent and desire to explore *without* coercing the patient regarding disclosure may be explained to family members. At a simple level one may simply need to confirm that the patient wishes to "defer" decision making to the family, although a richer exploration is encouraged. What to do if the patient states that she wants to know the truth or be in charge should be worked out before such an encounter. Most clinicians will want to be clear on certain ground rules such as not lying. If the patient requests to be informed, rather than simply tell, the clinician may change roles and act to facilitate improved communication between the patient and family.

Dealing with difficult dilemmas in real life cannot be done as proscriptively as the above might imply. The above is presented to offer the clinician some guidance as to how to explore and negotiate such a situation and to illustrate an approach to conflict that is hopefully more grounded in the "local moral worlds" of the participants than in ethical abstractions.

INTERCULTURAL COMMUNICATION

As the above discussion highlights, good communication is critical to the practice of medicine in general and palliative care in particular (82). Generic communication skills, such as the ability to listen, will not be discussed here. A number of recent texts explore intercultural communication in healthcare (83,84 and 85). Cultural aspects of communication specific to palliative care are beginning to be addressed in the literature and will be discussed further here (86,87).

The most obvious cultural communication barrier is language. Communication will be largely ineffective and prone to serious misunderstanding without competent translation. Relying on family members as translators, although sometimes unavoidable, is problematic, as messages between clinician and patient may be filtered (88). Professional medical translators, where available, are generally recommended although their use does not eliminate communication challenges (89). Skilled interpreters can do more than translate words. They may act as "cultural guides," facilitating broader understanding (90,91 and 92).

In considering language as a cultural barrier, the tendency is to view the other's language as the problem, something that needs only be *translated*. More difficult is recognition of the barriers intrinsic to the language of biomedicine. For example, the word *symptom* means a *clue* to something more important (usually the *disease*). A patient's complex, internal experience is translated into a vocabulary of symptoms as understood in the biomedical world, denigrating the primacy of this experience in the process. This linguistic bias handicaps those in palliative care who argue for the importance of "symptom management." An additional problem of the language of biomedicine is its scientific, technologic, and cognitive emphasis and relative neglect of more human concerns such as emotion. Patients and families often attempt to express their concerns through this biomedical language, trying to speak to us in our peculiar, foreign tongue. For example, distress in witnessing a family member near death may be expressed as a demand for some medical intervention such as intravenous hydration. In part this may be because people have become familiar with the bias of biomedicine to focus on *doing* rather than feeling. In hearing such a statement clinicians are prone to hear and respond to the technical aspects of the communication and ignore the affective subtext of distress (93,94). Thus, the specialized language of biomedicine can pose particular communication challenges for those attempting to address more human concerns, as palliative care leaders have rightfully advocated is necessary.

Cross-cultural communication in palliative care is particularly difficult because key content issues, such as serious illness, difficult decisions, and dying, are very sensitive for many people. Discussion of certain topics may frankly be taboo (95). In many cultures and for many people words have power. To speak of illness or dying is to increase the chance of illness or death occurring. Carrese, discussing Navajo difficulties with Western bioethics quotes a Navajo medicine man:

> In my practice, when I'm working with the patient, I am very careful of what I say, because any negative words could hurt the patient. So, with Western medicine, a doctor could be treating a patient, and he can mention death, and that is sharper than any needle (96).

Communication is far more than simple transmission of data from one source to another. Without some understanding of the context within which communication occurs, mutual understanding is impossible.

A branch of anthropology has focused on intercultural communication, based largely upon the pioneering work of anthropologist Edward Hall (97). Hall recognized that cultural contexts are not some inert boxes within which communication exists, but important aspects of communication itself. Hall and others have identified some cultures as being relatively high and others as relatively low in context (98). High-context cultures tend to depend more on the context of the situation than on verbal expression for communication. Context refers to things such as *who* is speaking to *whom*, the setting for the discussion, their relationship (including issues such as dominance, trust, or mistrust), the physical use of space and shared meanings. Nonverbal communication is closely linked to context. Context may be imbedded in verbal communication as well. The very different meanings in two expressions for dying, "kick the bucket" and "passing on," derive from shared contextual meanings (99). High-context people tend to become offended by overly direct verbal communication and a lack of attention to relationship building by low-context individuals. In contrast low-context cultures and individuals tend to stress direct verbal communication. Low-context people may become frustrated by vagueness and lack of direction in discussions with high-context individuals. Much of what is important to high-context people is frankly invisible to low-context people. Each cultural style has advantages and disadvantages. High-context groups are relatively stable, buttressed by a network of supporting relationships, but may have difficulty adapting to change. Low-context groups are less stable and more prone to social disruption, but better suited to rapid change and efficient data exchange. Science as a means of exploration and communication is low in context (100).

Biomedicine, arising from a Western, predominantly Northern European scientific tradition, is similarly very low in context. Although such a low-context approach may serve well where efficiency is needed and accurate transmission of data is required across cultures and languages, it becomes problematic when dealing with the more human issues commonly arising in palliative care.

Just as cultures may be higher or lower in context, so too can different human activities. Very personal, taboo, or dangerous activities tend to be more imbedded in context than impersonal affairs. Sexuality, for example, as a human activity is high in context (4, pp68–69). In the United States, we do not have to know much about verbal or nonverbal communication to understand the meaning implied in the context of a couple being in the back seat of a drivein movie. So too, for most of us,

serious illness, dying, and death are very personal and dangerous. The wealth of idioms across cultures lending context to dying as an activity, such as “passing away” or “kicking the bucket,” testify to the high-context nature of serious illness (99).

A major communication problem arises in palliative care when low-context clinicians practicing within the world of biomedicine deal with high-context events such as dying. Low-context clinicians in dealing with high-context encounters may benefit from first identifying encounters as such. Hints to a high-context encounter [such as a request for nondisclosure as discussed above (see the section Example of Nondisclosure)] include much indirectness in the conversation and the involvement of multiple participants. Although the low-context tendency is to “get down to business” and resolve a dilemma quickly, this approach often backfires in a high-context encounter when inadequate attention has been paid to relationship building. The low-context clinician may need to practice slowing down, and exploring and building a relationship prior to negotiating a specific course of action. This is often frustrating for the clinician. It may be very difficult for a low-context individual to appreciate that within a high-context world often the fastest, most direct path between two points is not a straight line, but a *curve*. To plunge too directly into sensitive discussions risks the relationship, fosters mistrust, and ultimately necessitates even more time for problem resolution.

EXPLANATORY MODELS AND ILLNESS NARRATIVES

Serious and life-limiting illnesses pose threats to personhood (16,17,19,20 and 21,101). Most of us—at least early in life—live optimistically, creating a life story for ourselves and our loved ones that ends, as should all fairy tales, with us living “happily ever after.” Serious illnesses are radical interruptions in these stories (16,17,102). The story has been interrupted and negated and a “blank page” introduced that invites filling (6, pp166–184). Sick individuals and involved others struggle to make some sense of this negation, to fill in the blank by interpreting the illness and eventually incorporating it into a revised life story that incorporates tragedy as well as triumph.

Kleinman introduced the term *explanatory model* as a means of understanding this process of interpretation (103). “Explanatory models are the notions that patients, families, *and practitioners* have about a specific illness episode” (104, p121) (italics mine). As this quotation points out, clinicians also have their own explanatory models for illness, most typically revolving around the concept of *disease.* Kleinman has suggested that eliciting a patient's explanatory model (and reciprocally reflecting and sharing one's one model) can further mutual understanding and help form a basis for collaborative decision making (104, pp227–251). He writes that in the face of illness two questions seem to dominate—*why* did this happen and *what* should be done about it. Specific questions useful in eliciting an explanatory model include the following: *What*— do you call the problem, do you think the illness does, do you think the natural course of the illness is, do you fear? *Why* do you think this illness or problem has occurred? *How* do you think the sickness should be treated, do you want us to help you? *Who*— should you turn to for help, should be involved in decision making? Such an exploration should not be *taken*, as clinicians often take a medical history, but should consist of *“empathic listening, translation,* and *interpretation”* (104, p228). In more recent writings Kleinman explicitly warned against using the explanatory model as a form of interrogation:

> I meant the explanatory models technique to be a device that would privilege meanings, especially the voices of patients and families, and that would design respect for difference. I intended it to be a *modus operandi* to get at what is at stake in suffering. . . . I saw explanatory models as a methodology for clinical self-reflexivity, for pressing against biomedical crystallizations, for laying hold of the sources of clinical miscommunication. I wanted to encourage the use of open-ended questions, negotiation, and listening, not the usual mode of clinical interrogation (3, pp8–9).

Exploring explanatory models is critical to effective communication. This is a process not only of listening to the patient, but of sharing and interpreting the clinician's personal explanatory model and the explanatory models of biomedicine as these apply to the patient's illness (105). Such exploration serves as a basis for collaboration and negotiation as to goals and choices. More concretely, exploration itself is often therapeutic.

Kleinman points out that explanatory models are not complete accounts of illness in and of themselves. They are part of broader *illness narratives,* which in turn are actively created out of rich life experiences in response to a disruption in life stories—a process of *integration* in the face of the disintegrating forces of illness (16,17,21). This process, of healing work in the face of certain unalterable realities of illness, seems to get at the heart of what palliative care is all about.

Kleinman suggests that an “ethnographic” approach is useful in exploring such narratives (104, pp227–251). Much like an anthropologist, the clinician is advised to approach the “culture” of the patient with friendly curiosity. How are symptoms understood by the patient? How are people with such an illness generally regarded and treated within that person's culture? What are the roles people are supposed to play out relative to such an illness? What nitty-gritty social forces are at work in shaping the story (such as poverty, the environment, or politics)? In the process of such an inquiry into the illness of the patient, the clinician/ethnographer interprets the story, in essence making sense out of the unknown or at times out of apparent nonsense.

GRIEF AND ILLNESS NARRATIVES

Illness narratives exist not as completed, published texts but rather as active processes of “writing” narratives in engagement with and creation of local worlds. For example, the active, creative aspects of illness narratives can be better understood by considering grief and mourning, which are strongly flavored by culture (38). Rando defines grief as a *reaction* to loss and mourning as “actions undertaken to cope with, adapt suitably to, and accommodate that loss and its ramifications” (106, p4). Rando stresses the *processes* of mourning, both in anticipatory mourning and bereavement, as means of coping and healing. Although the grief literature does not usually cite illness narratives, certain parallels are clear. Take, for example, Rando's writing about the psychosocial loss known as “assumptive world violation.”

> The assumptive world is the mental schema that contains all a person assumes to be true about the self, the world, and everything and everyone in it. . . . The assumptive world is the internal model against which the individual constantly matches incoming sensory data in order to orient the self, recognize what is happening, and plan behavior. (Parkes 1988). . . Any type of illness or death-related loss brings violations of those assumptive world elements predicated specifically upon the existence of the lost person or object. . . . (These models) are frequently shattered by and during life-threatening or terminal illness and constitute a main area of loss and major targets for intervention (106, p61–62).

It is not much of a leap to see the process described by Rando as an interruption in the life story and mourning as a process of creating a new life story that accommodates this “violation.” The “assumptive world” is itself a cultural world, as is the new world created in the process of mourning. Interventions taken to facilitate such mourning must be cognizant of the active process of narrative reconstruction, which occurs in a cultural context.

SUMMARY

Understanding culture and its relation to palliative care is challenging. Culture encompasses both the grandest and the most intimate aspects of human experience. Although biomedicine has tended to define illness as a pathophysiologic process distinct from personhood and culture, palliative care can afford no such luxury. A major challenge for palliative care is to use the tools and technologies so skillfully developed in the world of biomedicine in service of the person and the family, who experience illness and suffer in rich cultural contexts. Better understanding, both of the other's culture and our own, as well as cross-cultural skill development, should aid us in this task.

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COMMUNICATION AT END OF LIFE

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Palliative care aims to meet the disparate needs of patients and families during a time of life-limiting illness. Good communication is indispensable to uncovering patient and family needs and individually negotiating the goals of care. Everyone defines a good death differently (1), and whether patient suffering is caused by pain, nausea, unwanted medical intervention, or spiritual crisis, the common pathway to treatment is through a provider that is able to elicit these concerns and is equipped to help the patient and family address them.

Good communication brings real and tangible benefits. In patients with cancer, the number and severity of unresolved concerns has been shown to predict high levels of emotional distress and future anxiety and depression (2,3 and 4). Conversely, considerable evidence suggests that improved physician-patient communication correlates with improved health outcomes, patient satisfaction, and emotional well-being (5,6,7,8 and 9). For example, primary care patients exhibit decreased anxiety and are more satisfied with their physicians if they discuss advance care planning (9a). Finally, communication itself appears to be therapeutic, as simply telling one's story may improve objective health outcomes (10).

This chapter is designed to (a) review recent literature concerning health care provider communication, (b) survey basic communication issues relevant to palliative care, particularly the role of affect in communication, and (c) give the reader practical advice regarding some of the common topics that arise when caring for patients with life-limiting illness— giving bad news, discussing advance care planning, introducing palliative care, and talking about prognostic issues.

HEALTH CARE PROVIDERS DO NOT COMMUNICATE WELL

Unfortunately, the general quality of communication between health care providers and patients with life-limiting disease is suboptimal. Studies show that the discussion of bad news frequently does not meet patient needs or falls short of expert recommendations (2,11,12,13,14,15,16 and 17). Both physicians and nurses tend to underestimate cancer patients' concerns (18), and commonly do not elicit the full range of terminally ill patients' concerns, or attend to patients' affect (19). Rather than using facilitative communication techniques, such as open-ended questions or empathic responses when inquiring about psychosocial issues, they often block discussion of these issues by changing the subject or not attending to patients' emotional states (13,20). Even in a hospice setting, one study revealed that only 40% of patient concerns were elicited (21). As a result, cancer patients tend to disclose fewer than 50% of their concerns (20,21), which leads further to physicians' inaccurate assessments of patient distress (14). One large audiotape study of oncology visits with terminally ill patients found that physicians only dedicated 23% of their time to health-related, quality-of-life issues, including psychosocial concerns, and frequently missed opportunities to address issues that seemed to be most important to patients (22). Finally, physicians rarely talk with seriously ill patients about their goals, values, or even treatment decisions (23,24,25,26,27,28,29 and 30). A significant gap exists between the idealized model of provider-patient communication at the end of life and the reality of practice.

WHAT CAUSES POOR COMMUNICATION?

Why is the “state of the art” so poor? First, health care providers are not selected for their communication skills. Expertise in cognitive areas are not always positively correlated with empathy or an interest in understanding another person's experience. Second, until recently there has been little training regarding communication skills in general, not to mention communication about these difficult topics (31). For example, in a survey of over 3200 oncologists, few had any formal training in end-of-life care or communication skills. Oncology programs are not alone in devoting little attention to this subject. At both the medical school and residency level, inadequate attention is given to care of the dying (32). Among graduating students at two medical schools, only 48% said they had adequate role models for how to discuss end-of-life issues. At another school, 41% of medical students on a medicine rotation and 73% on a surgery rotation had never observed a staff physician talk with a dying patient. Finally, physicians have difficulty inquiring directly about the emotional status of dying patients because of their feelings about the patient or their own mortality. We will focus particularly on this issue.

Considerable evidence suggests physicians' personal feelings toward their patients are important to the doctorpatient relationship (33,34 and 35), and many have suggested that physicians' emotional responses to their dying patients may interfere with their care (36,37,38,39 and 40). Physicians dealing with dying patients are not objective observers. They are active participants whose beliefs and feelings influence the interaction. For example, a study of surrogate decision making found that physicians' predictions of their patients' wishes regarding life-sustaining treatment were closer to their own choices than to the choices expressed by their patients (41).

Caring for the dying may elicit significant stress in physicians and a variety of reactions, including guilt (“If only I'd convinced him to get that screening colonoscopy.”), impotence (“There's nothing I can do for her.”), failure (“I messed up. I'm a bad doctor.”), loss (“I'm really going to miss this person.”), resentment (“This patient is going to keep me in the hospital all night.”) and fear (“I know they're gonna sue me.”) (42). According to Spikes and Holland (38), many physicians have unconscious feelings of omnipotence, and troublesome responses stem from a physician's need to preserve his or her image as a “powerful healer” who can master any situation. Feeling that he or she has failed the dying patient, a physician may respond by acting defensively, wishing the patient would die (to avoid dealing with the patient), or treating too aggressively (to ensure that “everything has been done to save the patient”).

Empathizing with a dying patient often evokes anxiety about the physician's own mortality. Physicians respond by withdrawing (43) from terminally ill patients, avoiding threatening topics (15,20,44), employing blocking behaviors that distance them from addressing affective concerns of patients (45), or falsely reassuring them that “everything is OK” (38).

Empirical data support these claims about physicians' anxieties regarding death. Physicians score higher on death anxiety scales than other professional groups (46). They also find caring for terminally ill patients stressful. For example, in a survey of 598 oncologists, 56% reported being burned out and 53% attributed these feelings to continuous exposure to fatal illness (47). When caring for dying patients, physicians often report sadness, helplessness, failure, disappointment, and loneliness (48). These feelings, particularly if unrecognized, may affect patient care (49). A study of 25 pediatric residents explored the relationship between their orientation toward death and their response to a clinical vignette. Residents with a high death threat and anxiety scores were more likely to adopt avoidance and denial strategies for dealing with the vignette (50).

Although these issues are profound, awareness of their own emotional responses to caring for dying patients can help physicians begin to focus more objectively on the effect of their behavior on the patient.

BASIC COMMUNICATION SKILLS

Talking to dying patients is just like, and completely unlike, all other communication with patients. Whether one is explaining the implications of hypertension, or talking about impending death, basic principles of good communication are useful. The primary difference between these communication tasks is the meaning of the conversation to the patient and the provider and the attendant level of emotional significance. When the situation is more likely to make the patient (or physician) feel

vulnerable, sad, or inadequate, one should focus extra attention on the task. In this section we will address basic communication skills that are universal to all encounters.

A little effort spent on advance preparation can have a tremendous impact on the quality of the encounter. Whenever possible, important medical information, particularly bad or sad news, should be delivered during a scheduled meeting. This allows patients to prepare themselves for the type of information they will hear and to make sure that appropriate family members or friends are present. It also allows the physician to allocate the necessary time to the encounter and to come prepared with basic medical information and anticipating the most likely questions regarding treatment options, prognosis, and resources for support and guidance.

Communication best occurs face-to-face. Telephones accentuate physical communication difficulties and there is no opportunity to employ the benefits of nonverbal communication. Given that over 50% of communication is nonverbal, both parties operate at a disadvantage if they cannot see each other. The physician should sit at eye level and within reach of the patient. If possible, one's pager or cellular phone should be turned off, or at least on a quiet mode, and one should avoid interruptions.

Increasingly, we encounter non–English-speaking patients. One must absolutely employ the assistance of an interpreter in such settings. However, it is equally important to avoid using family members as interpreters. Not only does this run the risk of faulty translation or reinterpretation of the physician's statements, it also places family members into the uncomfortable position of being the physician and patient's spokesperson. The common practice of using bilingual young children as translators is particularly problematic. Most hospitals and health care facilities in regions with high numbers of immigrants employ professional translators or maintain lists of language skills among facility staff members.

Regarding the dialogue itself, considerable data exist from the medical and psychological literature to support certain general techniques that allow more accurate assessment of anxiety and depression and increased disclosure of concerns (19,51,52). One should maintain good eye contact, ask open-ended rather than closed-ended questions, focus on the patient's concerns as well as your agenda for the visit, respond to the patient's affect, ask about the patient's life outside of medicine and attend to psychosocial issues, and ensure that nonverbal behavior signifies attentiveness (Table 48-1). In contrast disclosure of concerns is inhibited by closed-ended or leading questions, focusing on physical aspects of illness, and offering of advice and premature reassurance (19).

Maintain good eye contact
Ask open-ended rather than closed-ended questions
Focus on the patient's concerns as well as your agenda for the visit
Observe and respond to the patient's affect
Ask about the patient's life outside of medicine and attend to psychosocial issues
Ensure your nonverbal behavior signifies attentiveness

TABLE 48-1. GENERAL COMMUNICATION SKILLS TO ENHANCE DISCLOSURE OF CONCERNS

One core precept is to not assume that one knows what is on the patient's agenda. For example, while many patients will want to discuss end-of-life issues, about 25% will not. This may have to do with cultural particularities or with how individuals cope with illness. Physicians are not very good at predicting which patients want more and which patients want less information. Instead of assuming, one should ask. For example, on a first visit one could say, “I want to touch base with you about how you want me to handle information we get about your illness. Some patients want to know everything that is going on with their illness, the good and the bad. Other people do not want as much information and want me to speak more generally. And some would really prefer I do not discuss bad news with them but want me to discuss these issues with their family. Have you thought about this?”.

Another important precept of communication is to “ask before telling.” Patients often carry misperceptions or incomplete information obtained from the popular media, folklore, or friends and family. It is easier to deal with this information if it is discussed directly. Thus it is usually helpful to ask patients about their understanding of their illness prior to educating them.

WHAT IS EFFECTIVE COMMUNICATION AT THE END OF LIFE?

According to dying patients, family members, and health care providers, goals for communication at the end of life include talking with patients in an honest and straightforward way, being willing to talk about dying, giving bad news in a sensitive way, listening to patients, encouraging questions from patients, and being responsive to patients' readiness to talk about death (17). Patients want physicians to achieve a balance between being honest and straightforward and not discouraging hope. For some this requires leaving open the possibility that unexpected “miracles” might happen, discussing outcomes other than a cure that can offer patients hope and meaning, and helping patients prepare for the losses they may experience. Although patients must receive adequate information to make informed choices, they wish to receive that information in an emotionally supportive way (53). Patients want to discuss emotional concerns but frequently are unwilling to bring them up spontaneously and may need to be prompted (54). Therefore, communication with patients at the end of life should be informative, patient-centered rather than physician-centered (55), and attend to patients' emotional needs. Many models have been proposed (56,57,58,59 and 60). In this chapter we will particularly focus on the role of emotions in such discussions.

ROLE OF AFFECT

Most difficulties in communication at the end of life are the result of inattention to affect. *Affect* refers to the feelings and emotions associated with the content of the conversation. Feelings such as anger, guilt, frustration, sadness, and fear modify our ability to hear, to communicate, and to make decisions. For example, after hearing bad news, most patients are so overwhelmed emotionally that they are unable to comprehend very much about the details of the illness or a treatment plan (12,61). Some studies have shown that emotion affects processing; people who are in negative moods may pay more attention to how messages are given than to the content of the messages (62,63). Thus when patients are experiencing high levels of negative affect and caregivers do not ameliorate this affect, patients may be less likely to receive health care providers' messages. Unfortunately, conversations between doctors and patients often transpire only in the cognitive realm; emotion is frequently not acknowledged or handled directly and physicians miss opportunities to do so (64,65).

Dealing with Physicians' Emotions

Physicians, as well as patients, experience many emotions as they care for people approaching the end of life. In addition to its effect on their own communication, physician affect plays an important role in patients' reactions to medical information. In one study, women were randomly assigned to view a video of an oncologist presenting mammogram results who was portrayed as either worried or not worried. Those watching the “worried” physician received less information, experienced higher anxiety levels, and perceived the situation as more severe compared with those watching the “nonworried” physician (66).

For physicians, the first step towards managing feelings of loss, helplessness, or anxiety is to acknowledge that they exist and to recognize that they are normal. When experiencing a strong emotion while interacting with a patient, one should ask oneself, “Where is this coming from?” Although it may be a result of what the physician brings to the encounter (e.g., one's own sense of mortality or how it makes one think of his or her grandmother who died), it may also be a clue into what the patient is feeling. Thus many doctors report feeling anxious when talking with a patient who has an anxiety disorder, or overly sad when talking with a depressed patient. If the physician gets a sense that he or she is reflecting the patient's emotion it may help to ask the patient about this (e.g., “I wonder if you're feeling sad?”).

If the emotion is a result of one's reaction to the encounter, the next step is to discuss this with colleagues or confidants. In most cases, however, patients do not benefit from hearing such thoughts. When considering sharing such feelings with a patient, a good rule of thumb is to ask oneself, “Am I doing this for me or for the patient?” If the answer is truly the latter, then it may be appropriate to share.

Dealing with Patients' Emotions

One barrier to engaging patient affect is the fear of being unable to manage the emotional response. This section will describe an approach to handling emotions that is

also likely to further elicit the sorts of patient concerns described earlier.

The primary goal when responding to emotions is to convey a sense of empathy. Empathy is the sense that “I could be you,” and is what patients are usually feeling when they comment about a physician that really cared for them (67). Robert Smith has created a useful mnemonic to recall four basic techniques to use when confronted by patient emotions, NURS (Name, Understand, Respect, and Support) (68). This discussion adds a final “E” for Explore. (Table 48-2).

Name the emotion
Understand the emotion
Respect or praise the patient
Support the patient
Explore what underlies the emotion

Adapted from Fischer GS, Tulsky JA, Arnold RM. Communicating a poor prognosis. In: Portenoy RK, Bruera E, eds. *Topics in palliative care*, Vol 4. New York: Oxford University Press, 2000, with permission.

TABLE 48-2. NURSE-ING AN EMOTION

Naming the emotion serves to acknowledge the feeling and to demonstrate that it is a legitimate area for discussion. Statements such as, “That seems sad for you,” can serve this purpose well, although one needs to be careful not to inappropriately label the patient. Therefore, naming is often best done in a quizzical fashion that does not presuppose the emotion (e.g., “Many people would feel angry if that happened to them. I wonder if you ever feel that way?”).

Expressing a sense of understanding normalizes the patient's emotion and conveys empathy. However, expressing understanding must be done cautiously to prevent a response such as, “How can you possibly understand what I'm going through? Have you ever had a stroke?” A typical statement might be, “Although I've never shared your experience, I do understand that this has been a really hard time for you.”

Respect reminds us to praise patients and families for what they are doing and how they are managing with a difficult situation. Offering respect defuses defensiveness and makes people feel good about themselves and more capable of handling the future. A useful statement might be, “I am so impressed with how you've continued to provide excellent care for your mother as her dementia has progressed.”

Support is essential to helping people in distress not feel alone. Simple statements such as, “I will be there with you throughout this illness,” can be tremendously comforting. Health care providers ought not feel the entire support burden on their shoulders—support offered can include other members of a team. For example, “We will send a nurse to your home to check in on you in a couple of days and if you'd like, I could ask the chaplain to visit you.”

Finally, patients will frequently make statements that deserve further exploration. For example, a patient may say, “After you gave me the results of the test, I thought that this is gonna be it.” A simple response such as, “Tell me more,” may help reveal the patient's fears and concerns about cancer that will be helpful in planning future treatment.

Hope in the Context of Palliative Care

Physicians struggle to promote hope in the patient with advanced disease and to support a positive outlook, fearing that discussing death may decrease patient hopefulness (17,69,70,71 and 72). As a result, they frequently convey prognosis with an optimistic bias or do not give this information at all (73). This is relevant to treatment choices; patients with more optimistic assessments of their own prognosis are more likely to choose aggressive therapies at the end of life (74,75). In turn, fearing the loss of hope, patients frequently cope by expressing denial and may be unwilling to hear what is said (76).

It is not clear that health care providers can either steal or instill hope. However, they can provide an empathic, reflective presence that will help patients draw strength from their existing resources. Physicians should recognize that it is not their job to “correct” the patient's hope for a miracle. The key question is whether the hope is interfering with appropriate planning and behavior. A patient who has completed his will and said his goodbyes but is still hoping for a miracle is different than a patient who is making longterm investments and does not plan for custody of a minor child despite a 3-month prognosis.

Physicians can respond in several ways (in addition to demonstrations of empathy discussed earlier). Acknowledging the hope may allow the physician and the patient to “hope for the best but prepare for the worst.” They can also recognize that people hope for many different things and leave space for patients to hope for outcomes and futures that are more likely to occur. One might say, “I know you are hoping that your disease will be cured. Are there other things that you want to focus on?” Or, “If we can not make that happen, what other shorter term goals might we focus on?” Finally, one can ask about what tasks are left undone as a way to get patients to begin to think in a shorter time course.

PRACTICAL SUGGESTIONS FOR SPECIFIC SITUATIONS

Communicating Bad News

Communicating bad news draws upon the skills discussed previously (see the section What Is Effective Communication at the End of Life?). Many protocols exist for the delivery of bad news, however the behaviors tend to be grouped into several key domains, preparation, content of message, dealing with patient responses, and ending the encounter (Table 48-3) (16,77). The primary elements of preparation have been addressed above (see the section Basic Communication Skills).

Preparation
Find out what patient knows and believes
Find out what patient wants to know
Suggest a supportive person accompany the patient
Learn about the patient's condition
Arrange the encounter in a private place with enough time
Content
Get to the point quickly
Fire “warning shot” (e.g., “I have bad news.”)
State the news clearly, simply, and sensitively
Avoid false reassurance
Make truthful, hopeful statements
Provide information in small chunks
Handle patient's reactions
Inquire about meaning of the condition for the patient
NURSE expressed emotions
Assure continued support
Wrap-up
Set up a meeting within next few days
Offer to talk to relatives/friends
Suggest that patients write down questions
Provide a way to be reached in emergencies
Assess suicidality

NURSE, Name, Understand, Respect, Support, and Explore (see Table 48-2).
From Fischer GS, Tulsky JA, Arnold RM. Communicating a poor prognosis. In: Portenoy RK, Bruera E, eds. *Topics in palliative care*, Vol. 4. New York: Oxford University Press, 2000.

TABLE 48-3. KEY ELEMENTS OF DELIVERING BAD NEWS

Content of Message

Knowledge of what the patient already knows or believes is extremely valuable to have prior to revealing bad news to a patient (77). This allows the physician to begin the explanation from the patient's perspective, aligning oneself with the patient and making communication more efficient and effective. The time that a test is ordered is a good time to assess this. One might ask, “Is there anything that you are particularly concerned about?” If the patient mentions a serious illness that might be present, the physician can follow up by asking what the patient's specific fears and concerns are.

When prepared to deliver the content of the message, the physician should begin by firing a brief “warning shot,” and then stating the news in clear and direct terms. One should avoid spending any time “beating around the bush” prior to sharing the news. After this brief exchange, the physician should remain silent and allow the patient an opportunity for the news to sink in. One can strike an empathic pose, maintain comfortable eye contact, and perhaps use a nonverbal gesture such as reaching out and touching the patient's hand. However, silence is imperative to allow the patient an opportunity to process the information, formulate a response, and to experience his or her emotions. Physicians who feel uncomfortable during this silent phase need to appreciate that the discomfort is rarely shared by the patient, who is engrossed in thought about the meaning of the news and thoughts about the future. Furthermore, very little that is said by the physician at this time will be remembered by the patient so it is best not to say it at all. If the patient makes no verbal response after, perhaps, two minutes, it can be useful to check in: “I just told you some pretty serious news, do you feel comfortable sharing your thoughts about this?”

Dealing with the Response

The remainder of the conversation should be spent primarily dealing with the patient's response. This includes using the NURSE skills to legitimize and empathize with the patient's experience. It is also important to explore the meaning the news has for the patient and to achieve a shared understanding of the disease and its implications.

For example:

MD: What is most troubling to you about having cancer?
PT: It's a death sentence—my mother died from cancer, my brother died from cancer. I guess it's my turn now.
MD: Given your experience, I can see how this is really scary for you. And cancer can be very serious. However, in your case, there are a lot of treatment options, and you have a good chance of surviving with this disease.
PT: So this won't kill me?
MD: I certainly hope not. And, I'll be there with you every step of the way fighting this illness.

Hopeful messages need to be tailored to patients' specific concerns, particularly addressing patient misconceptions and fears. Once patients' concerns have been explored, patients can be reassured more effectively. When effective treatment is available, this fact should be explained. When the treatment options are poor, hope may be found by alleviating patients' worst fears. Doctors may reassure patients that they will not be abandoned during their illness, that the doctor will remain available if things get worse, that everything will be done to maintain the patient's comfort, and that they will continue to watch for new treatment developments (78). Often people find hope and strength from their religious or spiritual beliefs, from having their individuality respected, from meaningful relationships with others, and from finding meaning in their lives (71). Exploring these with the patient over time may help to foster realistic hope. Although physicians may have a desire to make an overly reassuring statement to the patient right after revealing the diagnosis, hopeful statements that are truthful and that are made after taking the time to first explore the patient's concerns are more likely to be accepted by the patient (79). One can offer a realistic sense of hope, whether biomedical (“We'll keep our eyes open for new treatments and discuss them as they become available.”) or psychosocial (“I look forward to talking with you more about how we can help you live every day as fully as possible, despite this illness.”).

Patients may have specific questions about further tests, treatment options, and prognosis. It is important to respond to these seriously. However, many patients will suffer comprehension difficulties in such emotionally challenging situations. Information, particularly a plan, is helpful, as it allows the patient to reconceptualize the future as a safer, more predictable place. The exact details matter less than the clarity of the plan and the reassurance that the physician will be available. Give simple, focused bits of information, use nonvague language that patients can understand, carefully observe the patient's verbal and nonverbal reactions to what you say, and most important, avoid information-packed speeches.

Ending the Encounter

The clinician must end the encounter in a way that leaves the patient feeling supported and with some sense of hope. Support can be provided through meeting patients' immediate health needs and risks. One must treat pain and palliate other symptoms. Patients should be asked how they plan to cope with the news, and if their response raises any concerns about suicide this should be asked about directly and addressed. One should try to minimize aloneness through statements of nonabandonment and referral to other resources, such as support groups, counselors, or pastoral care.

Last, one should provide a specific follow-up plan: “I'd like you to keep a list of questions so I can answer them for you on our next visit this Tuesday. We'll talk about all your options again at that time . . . . Okay? And please feel free to call me.” The physician needs to remember that the goal of this conversation is not to leave a happy patient. That is rarely possible (or even desirable) after delivering bad news. Instead, one hopes to leave a patient who feels supported and cared for, and can look forward to a specific plan of action.

Advance Care Planning

Discussions about advance care planning encompass many goals. These include preparing for death and dying, exercising control, relieving burdens placed on loved ones, helping patients make decisions consistent with their values, and leaving patients feeling supported and understood (80). The first step in preparing to discuss advance care plans is deciding upon the appropriate goals for the discussion (81). What one hopes to accomplish will vary depending on the clinical situation (82). Advance care planning includes many different tasks: informing the patient, eliciting preferences, identifying a surrogate decision-maker, and providing emotional support. Frequently one cannot accomplish all of this in one conversation and focusing on the goals of the discussion allows the physician to tailor the encounter. Advance care planning is completed as a process over time that allows patients an opportunity for thoughtful reflection and interaction with others.

For a healthy, older patient, physicians might establish whom the patient would like to appoint as a health care surrogate. They might ask whether the patient already has a written advance directive and explore the patient's thoughts about dying and the general views about life-sustaining treatments. For a patient with a life-limiting chronic illness, the doctor might also discuss the patient's attitudes about specific interventions that are likely to occur (e.g., mechanical ventilation in severe chronic obstructive pulmonary disease). Finally, for a patient who will soon die, the doctor will shift the focus from future treatment in hypothetical scenarios to establishing what the goals should be for care provided in the present. In all cases, advance care planning can help patients prepare for death, discuss their values with their loved ones, and achieve a sense of control (80). It can help build trust between doctors and their patients so that when difficult treatment decisions arise, doctors, patients, and their loved ones can communicate openly and achieve resolution.

Initiating the Conversation

There are a number of ways to begin the discussion (81). Often, physicians can relate the topic to a recent serious event such as a hospitalization. Another way to begin is to ask about experiences with relatives or friends who have died. Many patients are likely to have observed serious illness closely and perhaps have had loved ones in some of the situations which the physician is describing. They are likely to have much information and misinformation about endof-life care and are likely to have thought about their own deaths. Opening a discussion in this manner can naturally lead to a discussion about how decisions were made and what the patient thought of that particular death. This will provide valuable insights into the patient's own values.

Providing Information

Patients must have adequate information to make informed decisions. It helps to start by asking patients what they understand about their medical illness. If the patient's condition is more serious than he or she realizes, then the physician will need to shift focus. The physician will want to put off discussing advance care planning, focusing the discussion instead on explaining to the patient the seriousness of his or her condition.

Studies indicate that patients are more interested in what the expected health outcome will be than in details about the interventions themselves (83,84). The primary reason for patients to consider withholding treatments is to avoid an outcome judged by them to be worse than death (85). The other reason is that the burden of the treatment, on themselves or their loved ones, outweighs the potential benefit. Therefore, patients should achieve an understanding of the impact of common, life-sustaining interventions on one's quality of life. In contrast, vivid descriptions of the nature of the treatments themselves (e.g., intubation, cardioversion, intensive care unit care) may alarm patients and be less helpful.

Eliciting Preferences

Patients state preferences after learning about potential options and evaluating these in light of their personal values. Values refer to deeply held beliefs such as a

desire for personal independence or the importance of a religious practice. By exploring patients' values and goals, clinicians can help them clarify their specific preferences. Sometimes one can ask explicitly about such values (e.g., “What makes life worth living for you?”). Alternatively, values may be elicited in the process of asking about specific treatment preferences. For example, after a patient makes a statement about end-of-life care (e.g., “I'd never want to be on one of those machines”), the clinician may respond by simply asking, “Why?” The answer to this question (e.g., “Because I never want to be a burden on my family or society”) may uncover a patient's core values that will impact greatly on treatment decisions.

Identifying what conditions the patient would find unacceptable can also help clarify a patient's preferences. A useful question is “Can you imagine any situations in which life would not be worth living?”(86). This question can be followed by asking what the patient would be willing to forgo in order to avoid such states.

For many patients, dealing with uncertainty is the most difficult aspect of decision-making. When doctors ask patients if they would want a particular treatment, like a ventilator, patients will often state that the treatment should be provided “if it will help me, but if it won't help me, don't do it.” Statements like this ignore the reality that physicians are often uncertain about the outcome. Everyone responds to uncertainty differently, and the patient's approach to this issue should be discussed explicitly as well. For example, one may ask, “What if we are not sure whether we will be able to get you off the breathing machine?” Depending on the patient's answer to this question, the doctor can explore what the chance of success needs to be in order to pursue aggressive treatment. Some patients will state that any possibility of recovery is worth pursuing while others will refuse curative treatment when the likelihood of recovery drops below a particular threshold (75). Some patients are comfortable using numbers talking about probabilities, others are less quantitatively facile (87,88 and 89). The patient's preferences should dictate the extent to which numbers are used in this discussion. Many patients will be satisfied, leaving it to the judgment of the physician and family members, with only general instructions. The option of a treatment trial is also a useful way to provide clarity in the face of uncertainty.

It is impossible to elicit meaningful preferences for every intervention in every possible situation. By focusing on a patient's values and goals, the physician can then help the patient make decisions about current or future treatments that are consistent with those goals. Discussions should move back and forth from preferences to reasons and values to information and back again, ensuring that the patient understands the implications of his or her stated preferences, and that the doctor understands the patient's values. In this way, when the physician is faced with an unanticipated clinical situation, he or she can use the patient's stated values and goals to help determine the appropriate course of action. In such discussions, it is frequently worthwhile to inquire specifically about some controversial treatments such as artificial nutrition and hydration. This is particularly true in states that require the patient's specific directive to withhold these treatments.

Patients and physicians often use vague terms that ought to be avoided. For example, a statement that a treatment should be continued as long as “quality of life is good” begs further clarification. How does the patient (or his or her surrogate, or the physician) define a good quality of life? In fact, it is always important to ensure that the patient and physician have a shared understanding of the conversation and its implications. Similarly, medical jargon should be avoided, one should always define technical terms, and patients must be encouraged to ask questions.

Choosing Surrogate Decision Makers

Identifying who is to act as the patient's health care proxy may be the most important outcome of a conversation about advance care planning. Does the patient wish this to be a single individual or an entire family? Given the literature demonstrating poor concordance between patient preferences and surrogate perceptions of those preferences, the clinician would be wise to stress the need for the patient to communicate with the selected proxy decision-maker (90). Patients should also be asked how much leeway their proxies should have in decision-making (91). Should proxies adhere strictly to patients' stated preferences or ought they to have more flexibility when making actual decisions?

These discussions can be emotionally difficult, even when they are welcome. It is important to draw upon the emotionhandling skills described earlier (see the section Role of Affect) and to acknowledge patients' feelings of sadness, fear, or anger, when they come up, and to validate those feelings by stating your understanding of their reaction. The physician can admit that the discussion can be difficult and support the patient by stating how helpful he or she has been in helping to understand his or her preferences. Another way doctors can provide support to patients is to assure them that they will do whatever they can to meet their goals (such as comfort) and to articulate what some of those things might be. In this way, doctors can assure patients that they will continue to care for them, even if they are in a condition in which they would not want life-sustaining treatment.

Communicating over the Transition

It is possible that the greatest communication challenges face physicians and patients as they discuss progression of disease, the transition from curative therapy to palliation and the referral for hospice care. Such times of transition involve the recognition of loss, redefinition of self-concept and social role, and great emotional stress. Patients are likely to feel sadness, anger, and denial. Physicians frequently have difficulty with such discussions because they feel a sense of failure, are worried that patients will feel abandoned, or that they will be overcome in the conversation by anxiety or despair (77). Furthermore, they may have their own unresolved issues about mortality or fear the patient's anticipated emotional response.

Again, it is useful to identify the goals of these conversations. They include eliciting emotional, psychological, and spiritual concerns, and providing empathic and practical support. Of course, it is also important to help patients acknowledge their illness and to make appropriate health care decisions such as enrolling in hospice. However, conversations should not be dominated by the physician's agenda, and patients must be given ample space to make decisions according to their own timetables. Physicians should employ behaviors that promote the sharing of concerns by patients and avoid behaviors such as reassurance that inhibit such sharing. See Table 48-4 for useful, open-ended questions with which one can initiate such conversations.

"What concerns you most about your illness?"
"How is treatment going for you (your family)?"
"As you think about your illness, what is the best and the worst that might happen?"
"What has been most difficult about this illness for you?"
"What are your hopes (your expectations, your fears) for the future?"
"As you think about the future, what is most important to you (what matters the most to you)?"

From Lo B, Quill T, Tulsky J. Discussing palliative care with patients. *Ann Intern Med* 1999;130:744–749, with permission.

TABLE 48-4. OPEN-ENDED QUESTIONS TO INITIATE CONVERSATIONS ABOUT DYING

As patients respond to these questions, the physician should continue to focus on the psychosocial and spiritual aspects of their illness and not allow the biomedical issues to dominate. It is important to avoid false reassurance (45). A particular form of response that can be extremely effective at these times is the “wish statement”(92). These are particularly effective in response to statements that appear to demonstrate significant denial of the severity of illness. For example:

PT: I'm going to get better. I know that this new chemotherapy they're offering at the university will make the difference.
MD: I wish that there was a treatment that would make this cancer go away.
PT: You mean that you don't think it will work.
MD: It's hard to come to terms with this, but, unfortunately, I don't believe it would help you overcome your cancer.
PT: I was afraid you might say that. What do we do now?
MD: There's a lot that we can do. Let's talk about what goals are most important for you right now.

The wish statement allows the doctor to demonstrate empathy toward the patient and align him or herself with the patient's hopes. Yet, at the same time it implicitly conveys the message that certain goals are unrealistic. In this way, the physician can address the patient's denial without losing the therapeutic alliance.

Dreaded Questions

Finally, it is useful to consider several of the questions that many physicians find most difficult to answer (e.g., “Why me?” “How long do I have to live?”). Responding to

such questions draws on the many skills described in this chapter and it is useful to keep several additional points in mind (93). The most important thing a physician can do is remain curious. One should not assume that one knows what the question is "really" about. A patient who is asking, "How long do I have?" may be wondering if she is going to live until Christmas, whether reports she has heard that the disease is fatal are accurate, or whether she is going to get out of the hospital. Acknowledge the question, but make sure you understand it before trying to answer (e.g., "That is a really tough question. What are you concerned about?"). It is also important to recognize that it is not necessarily the physician's job to solve the problem. Physicians do not have the answers to questions such as "Why me?" and may not be able to diminish the feelings of sadness and loss. What one can do is to acknowledge and normalize the feelings. In allowing patients to be heard, the physician may decrease a patient's sense of being alone in the disease, and thus decrease suffering. (An illustrative example is to imagine you have had a very bad day at work. When you come home and start to tell your family, how would you feel if they started to brainstorm different solutions to the problem? Most individuals would prefer their loved ones to acknowledge their day—"sounds like it was a really tough day"—rather than try to solve their problem.)

Having anticipated replies can be useful and several examples follow (58):

PT: How long do I have to live?
MD: I wonder if it is frightening not knowing what will happen next, or when.

This response acknowledges that underlying such a question is tremendous emotion, most likely fear. It will be important for the physician to give a factual response to this question. However, the patient will not be prepared to hear this response until the doctor has addressed his or her emotional concerns. The suggested answer above allows patients to speak about their fears and worries. When the physician needs to use a more factual response, the following is a way of being honest while maintaining hope: "On average, a person in your situation lives 3 to 4 months, but some people have much less time, and others may live over a year. I would take care now of any practical or family matters that you wish to have completed before you die, but continue to hope that you are one of the lucky people who gets a bit more time."

FM: Does this mean you're giving up on him?
MD: Absolutely not. But tell me, what do you mean by giving up?

Suggesting that a patient receive palliative care risks conveying a sense of abandonment. Physicians must be emphatic that palliative care and hospice are active forms of care that meet patients' varying goals at the end of life. However, further exploration of patients' or family's concerns about abandonment are important to understanding their perceptions and attitudes toward care at the end of life.

PT: Are you telling me that I am going to die?
MD: I wish that were not the case, but it is likely in the near future. I am also asking, how would you want to spend the remaining time if it were limited?

This wish statement helps the physician identify with the patient's loss. The previous sentence is an attempt by the physician to reframe the patient's understanding of the situation. He has acknowledged that the patient is dying, but now he seeks to understand what the patient's goals might be in light of this new information. Creating new goals in this way provides an outlet for the patient's hope.

Bereavement

Palliative care does not end when a patient dies. An awareness of bereavement can help one communicate with family and loved ones after the loss (94). Bereaved people ought to be encouraged to tell their stories of loss, including describing details of the days and weeks around the death of their loved one. Similarly, family members and friends benefit by recalling earlier positive memories of the person. Physicians can explore how the bereaved person has responded to the grief ("How have things been different for you since your husband died?"), and identify their social support and coping resources. One should not overlook the frequently enormous practical ramifications of loss such as financial difficulties, the need to leave a home, and transportation. Finally, physicians need to be aware that a significant minority of patients, 10–20%, have difficulty regaining their normal functioning after the loss. This syndrome—traumatic grief—seems distinct from depression and is characterized by excessive rumination and preoccupation with the dead individual.

Good communication skills are central to the provision of palliative care. The fundamentals of such communication are listening, recognizing one's own affective responses, attending to patients' emotional needs, and achieving a shared understanding of the concerns at hand. Specific tasks, such as delivering bad news, discussing advance care planning, helping patients through the transition to hospice care, and responding to difficult questions, require using these skills to ensure that patients' concerns are elicited and addressed, and they are informed and feel supported.

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49

PALLIATIVE RADIATION THERAPY

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WHAT IS PALLIATIVE RADIOTHERAPY?

Palliative radiotherapy (RT) is radiation treatment administered with the intent to palliate, i.e., improve symptoms and relieve suffering. Half the patients who are diagnosed with cancer will receive radiation therapy at some point in their course of disease, with a variety of intents—eradication of tumor, prevention of recurrence, or prevention or relief of symptoms. The intent of treatment may be curative, radical, adjuvant, palliative, or prophylactic. These terms are defined in Table 49-1. It is estimated that 40–50% of all RT courses are given with palliative intent (1,2). However, these figures may be an underestimate, as high curative doses of RT are sometimes used to control tumors for as long as possible or to prevent or relieve distressing symptoms rather than to actually eliminate the cancer.

Curative	Goal of treatment is elimination of tumor and cure of the patient.
Radical	Refers to intensity of treatment and dose of radiation. *Radical radiotherapy* typically refers to high-dose radiation treatment given with curative intent. However, this may or may not cure the patient (i.e., because of risk of metastases). May be given to provide local control of tumor, even if cure is not likely.
Adjuvant	A form of treatment used in conjunction with primary therapy implemented to aid the principal treatment regimen (e.g., radiation after complete surgical resection of all known cancer to prevent or minimize the risk of local or regional recurrence after surgery).
Palliative	Treatment that aims to relieve or alleviate symptoms. Focus is on symptom control and enhancing quality of life (noncurative).
Prophylactic	Any treatment regimen given with preventative intent. Examples include prophylactic cranial radiation (to prevent brain metastases by eliminating possible microscopic tumors in the brain) and prophylactic radiation of bone metastases (to minimize the risk of fracture).

TABLE 49-1. DEFINITIONS OF TERMS USED TO DESCRIBE THE INTENT OF RADIATION THERAPY

In an attempt to define the circumstances when it is most useful, this chapter will briefly define what is meant by “palliative radiotherapy,” review the rationale for its use, and discuss the evidence on which current palliative practice is based. As background, the reader is referred to the article by Mackillop (3), in which 10 rules for the practice of radiation therapy are presented (Table 49-2) based on the ethical principles that are used to guide the practice of medicine.

Palliative radiotherapy should be part of a comprehensive program of care.
The decision to recommend palliative radiotherapy should be based on a thorough assessment of the patient.
The decision to recommend palliative radiotherapy should be based on objective information.
The risk:benefit analysis should include consideration of all aspects of the patient's well being.
The short-term risks and benefits of palliative radiotherapy are more important than those that may or may not occur in the future.
The decision to use palliative radiotherapy should be consistent with the values and preferences of the patient.
The patient should be involved in the treatment decision to the extent that she or he wishes.
Time is precious when life is short.
Delays in starting palliative radiotherapy should be as short as reasonably achievable.
Courses of palliative radiotherapy should be no longer than necessary to achieve their therapeutic goal.
Palliative and curative goals should not be considered mutually exclusive.
Palliative radiotherapy should consume no more resources than necessary.

From Mackillop WJ. The principles of palliative radiotherapy: a radiation oncologist's perspective. Can J Oncol 1996;6(suppl2):5–11, with permission.

TABLE 49-2. RULES FOR THE PRACTICE OF RADIATION THERAPY

The radiation used in RT is part of the electromagnetic spectrum and consists of high-energy photons which are generated from a series of complex interactions in a linear accelerator (x-rays), or directly from the nucleus of a radioactive isotope, usually cobalt 60 (gamma-rays). This is “external beam radiotherapy” as opposed to “brachytherapy,” in which radioactive sources are directly into or close to the tumor in the patient's body. Definitions of these and other commonly used terms are contained in Table 49-3. Radiation can cure many radiosensitive cancers although frequently high doses are needed to eradicate all malignant cells in the tumor, such as 60–70 Grays (Gy) delivered in 1.8–2.0 Gy daily treatments or “fractions” over 6–8 weeks. Side effects of RT are related to normal tissue injury, both “acute” (during or shortly after completion of RT, e.g., mucositis, diarrhea) and “chronic” (months to years after RT, e.g., fibrosis). It is indeed the normal tissue tolerance that limits the dose of RT that can be delivered and results in complications following RT. There-fore, when the cancer cannot be cured and when the goal of treatment is relief of symptoms, it is logical to administer a lower total dose of RT over a shorter period of time.

TABLE 49-3. DEFINITIONS OF COMMON RADIOTHERAPY TERMS

The time between treatments allows normal tissue cells to repair and regenerate while also allowing tumor cells that may have been resistant to the previous fraction to become more radiosensitive by becoming oxygenated or moving to a different phase in the cell cycle. It has been shown that using small daily fractions, in sizes of 2 Gy or less, significantly reduces the risk of the patient developing late complications of RT treatment such as fibrosis or necrosis. These basic radiobiological principles may be less relevant to the application of palliative RT, as complete ablation of the tumor is not usually necessary to relieve symptoms, and late effects, which take several months or years to develop, are less relevant to a population with a short life expectancy. In addition, the use of lower than radical doses minimizes the risk of acute side effects such as mucositis. These acute effects are deemed to be a necessary evil in the treatment of a patient with curative intent, but in the palliative population, they can significantl affect quality of life over a time that may represent a substantial proportion of the patient's remaining life span.

Consequently, most palliative RT is practiced using lower total doses (frequently 8–30 Gy), larger daily fraction sizes (3–10 Gy/per fraction), and shorter total treatment times (1 day to 2 weeks) than RT with curative intent. The resultant side effects are less intense (due to lower total doses) and less prolonged (due to shorter overall treatment time). The actual effect on the tumor is greater than the same total dose administered in 2 Gy/fraction over a prolonged time period (as shorter overall treatment time avoids the problem of tumor repopulation). Nevertheless, there exists controversy about the best method of palliating with RT. This chapter aims to tackle that controversy by addressing the questions which are pertinent to this area—“the What, Why, Who, When, How, and Where of palliative radiotherapy.”

WHY SHOULD WE CONSIDER PALLIATIVE RADIOTHERAPY?

Palliative RT is very effective in relieving pain and many other symptoms related to local effects of cancer and metastases, and is usually well tolerated. The traditional indications for palliative RT are illustrated in Table 49-4. In general, palliative RT can be used to treat both primary tumors and localized metastases, providing that the lesion being irradiated is directly responsible for the production of a symptom. A thorough knowledge of treatment alternatives is needed, with weighing of the toxicity and likely symptom response to other palliative measures. If the patient's symptoms are well controlled medically, it is not always necessary to irradiate, although in most cases there are significant benefits to be gained if the radiation treatment leads to a decrease in drug requirement (e.g., opioid analgesics), and therefore fewer side effects (e.g., constipation).

Pain relief (bone metastases, lung cancer causing chest pain, tumors causing nerve root and soft tissue infiltration)
Control of bleeding (hemoptysis, vaginal and rectal bleeding)
Control of fungation and ulceration
Relief of impending or actual obstruction (esophagus, large airways, rectum)
Shrinkage of tumor masses causing symptoms (e.g., brain metastases, skin lesions)
Oncological emergencies (spinal cord compression, superior mediastinal obstruction)

TABLE 49-4. INDICATIONS FOR THE USE OF PALLIATIVE RADIOTHERAPY

Palliative RT typically causes only mild and transient side effects, due to the lower total doses of radiation commonly employed. It is usually tolerated well by all but the most infirm patients. However, as many side effects of radiation therapy do not usually develop until after therapy is completed, it is important to bring this fact to the attention of those caring for patients after radiation treatment.

WHO SHOULD RECEIVE PALLIATIVE RADIOTHERAPY?

The essential axiom of palliative RT is that it should be used for patients who have local symptoms that can be attributed to the presence of a malignant tumor. This could be extended to include patients deemed to be at risk of the development of such symptoms. There are few contraindications to palliative RT. Many patients deemed not suitable for radical treatment on the grounds of poor performance status, coexisting medical conditions, or disease extent may benefit from palliative RT. For example, patients with poor lung function and limited respiratory reserve not able to undergo surgery or radical RT because of the risk of severe respiratory impairment may still benefit from low-dose thoracic RT with its consequent lower risk of toxicity. Similarly, patients with collagen vascular diseases, who often have exaggerated and severe reactions to RT, may be considered for palliative RT, although the risk-benefit ratio of the treatment needs to be thoroughly discussed. Are there patients whose disease has progressed to the point where RT is no longer worthwhile? Radiation may indeed not be appropriate for bed-bound patients in the last stages of their illness, who may not live long enough to benefit from treatment. However, it should be noted that physicians are notoriously bad at estimating patients' life expectancy (4). If a patient's condition is a consequence of severe pain and/or large doses of opioid analgesia, it may be possible to achieve meaningful benefit, bearing in mind that symptom relief will usually take at least 2–4 weeks to become apparent (see the section Lung Cancer). In such situations, the use of “one-stop-shop” approach, where a patient can be assessed, planned, and treated with a single fraction all on the same visit, may be extremely useful.

There is a common misapprehension that once a patient has received RT to a certain area this cannot be repeated. There is no doubt that if a patient has previously received radical treatment, then it is impossible to give a second high-dose course to the same area. However, in the palliative situation, when an increased risk of late radiation complications is less of an issue, it may be feasible to administer low-dose RT to a previously treated area. It is certainly possible to repeat low-dose treatments more than once depending on the location of the tumor. However, if a patient has failed to derive any benefit from an initial short course of palliative RT, further radiation treatment is unlikely to be useful.

WHEN SHOULD PALLIATIVE RADIOTHERAPY BE GIVEN?

Prevention of Symptoms

In the situation where a patient has an incurable cancer that is asymptomatic, treatment may be deferred until symptoms arise, although this should be discussed with the patient. There is one randomized clinical trial that would support this approach (5), in which 230 patients with incurable lung cancer but no symptoms that required immediate radiation were randomized to palliative radiation (17 Gy in 2 fractions) or observation (i.e., radiation at time of symptomatic progression). After a 6-month follow-up, patients in the radiation arm were no more likely to be free of chest symptoms (cough, dyspnea, etc.) and no more likely to survive than patients in the observation arm. One-third of patients in the observation arm never required radiation (chemotherapy was not utilized either). Thus, use of radiation to prevent potential symptoms (of lung cancer) is not supported by evidence. Many patients are unhappy about a “wait-and-watch” approach and would prefer to receive active treatment. Many radiation oncologists have admitted that they do use palliative RT to “give hope” (6), although in such cases, the benefits may be minimal and patients may still be exposed to side effects. Despite the lack of evidence, prophylactic (preventative) palliative radiation may be used if the physician feels the patient is at high risk of developing fracture, cord compression, airway obstruction, or superior vena cava compression.

Treatment of Symptoms

There is no threshold of symptom severity that a patient needs to cross to require palliative RT. Treatment is equally useful whether the disease is producing mild or severe symptoms with little difference in palliative effect if treating a small or large-volume tumor. On some occasions, such as with patients with pain from multiple bone metastases, it may be more appropriate to treat with analgesics as this may cause better overall relief with less side effects than RT. Some patients may become completely pain free if their analgesics are adjusted appropriately. In those circumstances, it may be possible to defer radiation therapy.

Radiotherapeutic Emergencies

A true radiotherapeutic emergency is when failure to deliver treatment within a few hours or days could result in death or catastrophic irreversible damage. Severe pain,

distressing as it may be to the patient, is not an emergency, although it should be treated with great urgency. RT cannot produce pain relief immediately; thus, pharmacological measures are essential while RT is being organized and delivered. Table 49-5 lists indications for emergency RT in a large academic cancer center in Canada, the Princess Margaret Hospital, Toronto. In these circumstances, the patient should be seen by a radiation oncologist on the same day the lesion is diagnosed, and appropriate treatment should be started promptly.

Established spinal cord compression
Established superior vena cava obstruction
Life-threatening lower airway obstruction
Life-threatening hemorrhage
The following critical complications of radioresponsive tumors:
Ocular compression with blindness
Peripheral nerve compression, including cauda equina syndrome, with established motor dysfunction
Life-threatening renal insufficiency caused by kidney infiltration or ureteric obstruction
Life-threatening mass brain lesion
Malignant hypercalcemia refractory to other measures where radiotherapy constitutes appropriate definitive treatment
Progression of cancer documented following decision to treat with radiation therapy

[a]As identified by The Department of Radiation Oncology, Princess Margaret Hospital, Toronto, Canada, 1998.

TABLE 49-5. SITUATIONS REQUIRING THE EMERGENCY USE OF RADIATION THERAPY, PROVIDING NO OTHER TREATMENT IS APPROPRIATE [a]

Although RT should be administered without delay, relief may not be immediate. The time course for the benefits of RT depends on the situation but is rarely less than a few days. With the exception of a few very radiosensitive tissues and cells, such as lymphocytes, RT does not cause immediate cell death, but rather leads to failure of cells to divide, which then die at their next scheduled division. This is the reason why both the beneficial effects and the acute toxicities of RT take several days to become manifest. Occasionally, when treating bone metastases, large-fraction, wide-field treatment, such as half-body irradiation (HBI), can produce same-day benefits, but this is not the norm.

Opportunity Cost

Although individual radiation treatments often take only 10–20 minutes to deliver, time spent traveling and waiting for treatment can add up to several hours. A protracted course of RT, especially for patients living some distance from the treatment center, may occupy the vast majority of their waking hours. “Time is precious when life is short” (3). For each individual patient, the benefits of the treatment need to be compared with the cost in terms of lost opportunities for them to spend their remaining days as they choose (7). Although it appears likely that large single fractions are as efficacious as longer courses in many situations (see the section How Much Radiation Should Be Given?), if they are not, they may still be appropriate in patients when the opportunity cost of a two-week treatment would be extremely high. Any reduction in palliative benefit would be at most minimal, and concerns about the duration of the effect of single treatments are probably not relevant in patients with extremely limited prognosis.

HOW MUCH RADIATION SHOULD BE GIVEN?

Fractionation schedules for palliative radiation therapy have evolved based on clinical experiences rather than as a result of careful science. Although experimental treatment models have been developed and continue to be refined to increase the understanding of the effects of total dose, fraction size, and treatment time on outcome for radical courses of radiation therapy, until recently there has been minimal literature published on how these variables influence noncurative radiation therapy. Many palliative fractionation regimes exist because of physicians' personal preferences, often based on wide-ranging (and occasionally dubious) influences, such as departmental policies, machine availability, training, and concern about acute and late side effects (8).

Initially, schedules were developed pragmatically by physicians who realized that (a) a full radical dose of radiation was inappropriate in a patient who could not be cured, (b) symptoms could be significantly relieved by smaller total doses, and (c) shorter treatment times were more convenient for patients and their families. In 1948, Paterson at the Christie Hospital in Manchester recommended that palliative radiation be given over 1, 4, or 8 days and that “a useful palliative dosage was one-half or better still twothirds of a tumor lethal dose” (9). In 1966, in the first edition of Fletcher's textbook, it is recommended that doses ranging from 20 Gy in 5 fractions (long bones, vertebral column), through 30 Gy in 10 fractions (pelvis), to 40 Gy in 15 fractions (mediastinum) should be deployed (10). Neither author can substantiate these recommendations with data, but they are the foundations for palliative RT practice in Europe and North America.

Most literature on the subject was purely descriptive in nature until the last 10 years. Very few controlled clinical trials were carried out and palliative prescriptions were almost entirely based upon physicians' clinical experiences or those of their seniors. In addition, financial considerations have taken on a greater importance, especially in the last few years, with demand for radiation therapy often outstripping supply in publicly funded health systems. This has been reflected in an increasing tendency to use shorter and cheaper radiation treatment regimes. In privately funded health systems, such as in the United States, there are fewer constraints; in some situations, the physicians are remunerated on the basis of the number of fractions of treatment delivered. Thus, there may be pressure to prolong treatment times. However, audits of patterns of palliative RT practice in the last 15 years have stimulated much debate and increased research comparing different palliative prescriptions for various clinical scenarios.

WHERE IN THE BODY CAN PALLIATIVE RADIOTHERAPY BE EFFECTIVE?

When patients have cerebral metastases, palliative RT usually involves a course of treatment to the whole brain even if the patient has only one or two lesions confined to one part of the brain. However, patients with metastatic cancer in bone may only receive RT to part of their hemipelvis, even though they have disease involving all the pelvic bones. Why does this apparent paradox exist?

In the latter case, the decision can be explained by the fact that the larger the volume of tissue irradiated, the higher the risk of toxicity. If a patient is suffering pain only in the right ischium, then it is preferable to treat just this area rather than the entire pelvis, which would expose the patient to increased likelihood of acute side effects such as diarrhea, nausea, and vomiting. For the patient with cerebral metastases, there are likely to be occult micrometastases elsewhere in the brain, and thus treatment is aimed at not only relieving symptoms but also reducing the chance of future relapse (11).

The following sections deal with the sites most commonly irradiated palliatively. Non–small cell lung cancer (NSCLC) is the primary tumor most commonly treated with palliative intent. Bone and brain are the most common sites of metastatic disease for most cancer types and occupy a large percentage of the workload of a typical RT department. RT can also be useful to palliate pelvic disease, lymph node metastases, and spinal cord compression. Although liver metastases are common, they are less often treated with RT due to the toxicity of irradiating large volumes of hepatic tissue even to relatively small doses. Other measures are more commonly employed. Nevertheless, some centers do advocate the use of hepatic irradiation in patients with symptomatic, nonchemotherapy responsive liver metastases (12).

Lung Cancer

Lung cancer is the most common cancer in North America and the most common cause of cancer deaths in both men and women. The majority of patients either present with stage IV (metastatic and incurable) disease or develop metastases some time after the initial diagnosis. Although advances have been made with palliative chemotherapy, palliative radiation continues to play an important role in the management of endobronchial or extrinsic lesions causing atelectasis, postobstructive pneumonia, shortness of breath, cough, hemoptysis, pain, and large airway obstruction. RT is not effective at relieving shortness of breath that results from widespread or parenchymal disease, pleural effusion, or lymphangitic carcinomatosis. Symptoms due to nerve compression (e.g., superior sulcus/Pancoast tumors and intercostal neuropathic pain) are more difficult to palliate and may require high doses of radiation aimed at eradication of the tumor.

The relevant issues in assessing palliation in patients with lung cancer are the following: (a) symptom relief, including the rapidity of onset of symptom relief; the degree of relief (partial or complete improvement), and duration of symptom relief; (b) whether the patient has only one symptom or a conglomerate of symptoms (e.g., hemoptysis is easier to palliate than dyspnea); (c) the toxicity of treatment; and (d) any change in the patient's performance status. Obviously, the interplay of these issues is complex, and most research studies only attempt to measure some of these variables.

Numerous palliative RT trials have been performed, and some are highlighted in Table 49-6 (13,14,15,16,17,18,19 and 20). No dosefractionation schedule has to date demonstrated a clearcut advantage in terms of palliation, and until the mid-90s, there was no survival advantage to any of the regimens either (13,14,15,16,17 and 18). The third Medical Research Council study (19) was intriguing in suggesting that a higher RT dose (39 Gy/13 fractions) may result in prolonged survival in good

performance status patients, in comparison to 17 Gy/2 fractions. Given the wide variation in management of locally advanced lung cancer across countries and continents (21,22,23 and 24), many similar patients as those entered on the Medical Research Council study would likely be managed with combined chemo-RT with “curative” intent in the United States and elsewhere.

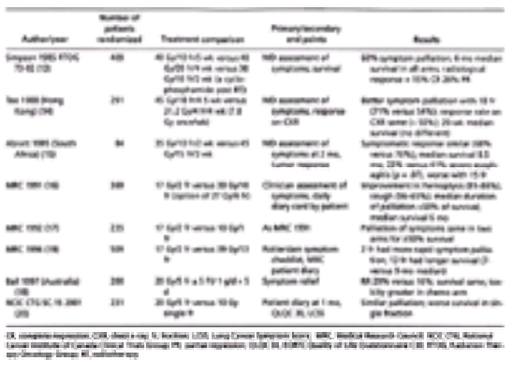

TABLE 49-6. SELECTED RANDOMIZED CLINICAL TRIALS OF PALLIATIVE RADIATION FOR LUNG CANCER

The palliation provided by thoracic RT is considerable. Many but not all studies have suggested that less protracted radiation protocols (including 17 Gy in 2 fractions 1 week apart and 10 Gy in a single fraction) (17) provide better palliation, i.e., equivalent symptom control with less toxicity and less burden to the patient and family. Using shorter treatment protocols, approximately 80–85% of patients report improvement in hemoptysis and 60% improvement in cough. Pain improved in two-thirds of patients. On average, symptom relief lasted for 50% or more of the patient's survival time. However, defining and analyzing symptom palliation in lung cancer is complex, as the effectiveness of palliative radiation may be related to the initial severity of the symptom (25). Timing of assessment is also important (26). A standard definition of palliation is lacking. These methodological concerns, although relevant to clinical trials, do not present an obstacle to recommending palliative RT in clinical practice. Chest symptoms caused by tumor mass, obstruction or invasion, such as cough, hemoptysis, collapsed lobe, pain due to vertebral or chest wall invasion, superior vena cava obstruction and such, are likely to improve with short or intermediate RT fractionation schedules, with mild to modest toxicity. External beam RT remains the gold standard form of palliative RT for lung cancer, but in patients who have already received such treatment and in cases where the tumor is causing obstruction of a major airway, direct insertion of radioactive sources into the bronchial lumen (endobronchial brachytherapy) may be considered. The response rates reported vary from 70–90% in appropriately selected patients (27).

Bone Metastases

RT remains the gold standard for palliation of painful bone metastases. A review of retrospective studies of palliative RT for bone noted that response rates reported varied from 65–100% (28). Noteworthy was the use of both single fractions, in doses as high as 18 Gy, and more radical fractionation schemes, e.g., 50 Gy over 5 weeks. However, the response criteria used in these reports were variable and included subjective interpretations of patients' charts. No consistent definitions of the terms “complete” or “partial relief” of pain in the context of RT for bone metastases currently exist.

Recently, these high responses have been questioned. In randomized trials where more stringent criteria are used, the response rates are lower, typically 30–70%. A recent meta-analysis by the Cochrane collaboration (29) found that palliative external beam RT produced complete pain relief at one month after treatment in only 25% of patients. There also exists considerable controversy over the appropriate scheduling of RT, with many oncologists in Europe advocating short courses of treatment, often only a single fraction, whereas many North Americans still employ more protracted regimes.

The first evidence for the benefit of short, hypofractionated treatments came from a Radiation Therapy Oncology Group (RTOG) trial, first published in 1982, which randomized over 1000 patients between a 15- or a 5-fraction regime (for solitary metastases), or 10- or a 5-fraction prescription (for multiple metastases). The primary end point was pain relief, prospectively collected but physicianassessed with no measures of toxicity. The results of this trial were published twice, causing confusion. In the first analysis (30), it was concluded that the low-dose, shortcourse schedules were as effective as the high-dose, protracted programs, but the subsequent reanalysis (31) came to the completely reverse opinion (i.e., that more is better). In retrospect, the design of this study was flawed and the contradictory results of the two analyses make any interpretation extremely difficult.

In the last 20 years, more studies have been performed and published. Price (32) randomized 288 patients, with life expectancy more than 6 weeks, to 8 Gy single fraction or 30 Gy over 2 weeks. Pain was evaluated by selfassessment using a validated tool, and the analgesic requirement was recorded. End points included partial response, defined as an improvement in pain score with some or reduced analgesia, and complete response, defined as no pain, no analgesia. There were no differences in total pain relief, rates of pain relief, or in duration of response in those who responded. Although toxicity was not specifically reported, there was no difference in acute side effects. Other recently published trials (33,34 and 35), the Cochrane meta-analysis (29), and a recently published consensus statement (36) all support the hypothesis that single fractions are equally effective as multi-fraction treatments.

Nevertheless, the results of a recently presented Canadian trial are interesting, showing superior pain relief at 3 months in patients treated with 20 Gy in 5 fractions (46%) as compared to 8 Gy in 1 fraction (31%). The end point used was patient self-report of pain relief without an increase in analgesics. However, if the proportion of patients reporting any pain relief was recorded, irrespective of whether their analgesics changed, the response rates were identical in the two arms (71% v. 72%) (37). This suggests that higher doses of RT given over prolonged periods may indeed have a greater biological effect but that this can be compensated for by analgesics. This result illustrates the need to define end points. Wu has demonstrated that there is no current agreement on how to report the results of such studies (38). Both he and the recent consensus statement (36) have identified the need for universally accepted definitions in this area.

Although a 1993 survey of UK oncologists indicated that 67% of British oncologists used single treatments for bone metastases (39), recent surveys of their European, Canadian, and Australasian counterparts demonstrate that single fractions are used by only 11%, 16%, and either 15% (breast primary) or 45% (lung primary) of respondents in those areas (40,41 and 42). These surveys show that despite a willingness to use single fraction treatments in some patients because of convenience and efficacy, there are still concerns about duration of response, acute complications, and patient tolerance. In health care systems where the physician is remunerated on the basis of the number of fractions of treatment delivered, there could even be a financial incentive to prolong treatment times, contrary to the principles listed in Table 49-2.

“Wide-field” radiation therapy can be given to patients with widespread bony disease, using either HBI or radioactive isotopes such as strontium-89. The response rates and duration of response are comparable to those achieved with local radiation, although one study suggests superior results from fractionated HBI in terms of duration and need for retreatments (43). At present the efficacy of strontium, used either alone or in conjunction with local radiation, is confined to the treatment of bone metastases from prostatic cancer, as it has an affinity for osteoblastic lesions. There is evidence that it is beneficial in both the treatment of known painful metastases and the prevention of future lesions, and further research is ongoing, in particular using newer isotopes such as rhenium-186 and samarium-153.

Side effects from palliative RT for bone metastases will vary depending on the area of the body being treated, but nausea and vomiting may be common, especially in patients receiving treatment to the thoracolumbar spine. It would appear from studies utilizing 5-HT3 antagonists that the incidence of acute side effects, especially emesis, is similar for both single fraction and multi-fraction treatment regimes. There appears to be little risk of developing complications within the actual bones treated, as in one British trial there were no differences in the numbers of fractures or incidences of paraplegia developing in a treated area (44). For HBI, toxicity tends to increase with dose, ranging from 30–60% gastrointestinal toxicity, 20–40% hematological toxicity, and occasional pulmonary toxicity, while with strontium trials there is no significant gastrointestinal toxicity, and hematological effects, although not uncommon, are usually mild.

It is not standard practice to prophylactically irradiate all bone metastases, whether or not they are painful, but there may be benefits from irradiating if they are at risk of fracture. The criteria defined in the orthopedic literature (45) (lytic lesions greater than 2.5 cm in diameter involving the cortex) are for lesions for which surgery should be considered, but RT may also be of benefit. In breast cancer patients, it has been noted that although RT to lytic bone metastases gives rates of pain relief of 70–81%, the radiological reossification rates are 17–31% (46,47). However, in a series of 59 patients with nonfractured lesions treated primarily with RT, only four developed subsequent pathological fractures, two of which occurred during the time of radiation. Thirty-nine of those 59 patients were classified as being at high risk, but the only fractures that occurred in this group were the two that developed during treatment. Therefore, RT may be effective for initial management of patients with high-risk bone metastases from breast cancer. Nevertheless, it would seem prudent that both the radiation oncologist and orthopedic surgeon assess patients at risk for pathological fractures. If fracture does occur, most patients will receive “adjuvant” radiation, although the value of this practice has never been demonstrated. Regimes used in this situation are based on those used to treat pain, but it is not clear whether the shorter hypofractionated regimes are as effective as longer courses in producing reossification. There may be a subset of patients, perhaps those who are completely ambulatory and pain free following surgery, who do not require

additional radiation, especially if they have a poor prognosis from their underlying malignancy (e.g., lung cancer).

Brain Metastases

Solitary brain metastases can be treated by surgical resection. Several small randomized trials (48–84 patients) have compared resection followed by radiation to RT alone, with improved survival in the surgical arm in two of the studies (48,49 and 50). An alternative to surgical resection is stereotactic radiation, also known as radiosurgery, or “gamma-knife,” i.e., external beam radiation with multiple beams from multiple directions, so as to concentrate the radiation dose to a limited area of the brain. Only one very small (N = 27) randomized trial of stereotactic radiosurgery plus whole brain radiotherapy (WBRT) versus WBRT alone has been published to date (51). Two large-scale, cooperative group clinical trials that are currently under way or are soon to be completed will contribute more evidence for the role of stereotactic radiosurgery boost after WBRT for one to three brain metastases (a trial conducted by RTOG), and the role of radiosurgery vs. resection and WBRT following radiosurgery (a European Organi- zation for Research on the Treatment of Cancer trial).

The majority of patients with brain metastases present with multiple metastases and are not candidates for limited radiation. Whole brain external beam RT is usually recommended, although steroids alone may be an option in patients with very limited life expectancy (52). It has not been clearly established whether RT is beneficial in asymptomatic patients, although prevention of neurological deterioration is a frequently cited reason for RT. The RT fractionation schedules that are utilized include 40 Gy in 20 fractions, 30 Gy in 10 fractions, 20 Gy in 5 fractions, and 17 Gy in 2 fractions. In a number of randomized studies comparing these various RT schedules (53,54,55,56 and 57), no difference was observed in response rate and survival, although a quicker response was often seen with shorter fractionation schedules. Approximately 50–90% of patients reported relief of neurological symptoms, and 50% of patients had functional improvement; a distinction between the effect of steroids versus RT was not made. These assessments were for the most part done by medical personnel rather than by direct patient report; median survival was 15–20 weeks. Patient selection for RT is clearly important, as in a large multicenter British study comparing 12 Gy in 2 fractions to 30 Gy in 10 fractions (57), one-third of the 533 patients randomized were too ill or dead at the one-month follow-up assessment.

Efforts at improving the outcome of palliative brain RT continue, especially in patients with a somewhat longer life expectancy. These efforts are aided by a recursive partitioning model derived from analyzing outcomes of patients in the RTOG studies, which has identified three prognostic strata on the basis of patients' age, performance status, and the presence or absence of extracranial cancer (58,59). This model classifies patients under 60 years of age, with Karnofsky performance status of 80–100, and no cancer elsewhere, as having the best prognosis (group I, 7 months median survival). Patients lacking one of the above criteria fall into an intermediate prognosis group (group II), and those not satisfying two or more criteria have a poor outcome and are less likely to benefit from treatment (group III). If treatment is indicated for patients in this group, a short course of palliative RT is usually employed. For groups I and II, more aggressive treatments being explored include accelerated or hyperfractionated RT, whole brain RT followed by stereotactic boost (a current RTOG study), and utilizing new radiosensitizers such as Gadolinium texaphyrin (60). Some of these strategies are showing promising initial results although the real benefit will have to await the completion and maturation of randomized clinical trials currently in progress.

Advanced Pelvic Malignancies

Patients with locally advanced, inoperable, or recurrent rectal and gynecological cancers frequently develop distressing symptoms such as pain, bleeding, and mucous discharge. RT is commonly employed to palliate these symptoms and although it is undoubtedly effective in a significant number of cases, there are few published data that detail the probability of benefit, nor is there information on the appropriate fractionation. A review of the role of RT for recurrent rectal cancer estimated that 70–90% of patients receiving RT for pain relief derived benefit at least initially, with 23–50% having symptom control for 6 months. A range of doses were used to achieve these results; it was not possible to assess the optimal regime, and the authors could not discern any difference between lower and higher doses in terms of symptom relief (61).

Treatment approaches are variable and range from the use of large fractions of up to 10 Gy, often repeated at intervals (62,63), to more conventionally fractionated highdose treatment, such as the 50 Gy in 25 fractions (64). An RTOG study of 10 Gy fractions given with the radiosensitizer misonidazole projected an increased risk (41%) of grade 3/4 complications in those who survived 12 months (65). Nevertheless, the use of large single fractions remains commonplace, especially for patients with poor performance status or with limited life expectancy. Other regimes commonly used include 20 Gy in 5 fractions, 30 Gy/10 fractions, 40 Gy/16 fractions, and for patients with good performance status with no disease outside the pelvis, doses up to 50 Gy can be employed.

Lymph Node Metastases

Involvement of lymph glands by metastatic cancer is common, causing airway or nerve pain or patient distress through their appearance or by interfering with normal daily activities.

One of the most significant complications of malignant lymphadenopathy is superior vena caval obstruction (SVCO). SVCO causes facial and neck swelling, headache, dyspnea, chest wall vein distention, and occasionally syncope. It is usually due to compression of the SVC by mediastinal lymphadenopathy. Most cases (80%) are due to malignancy with the most common underlying diagnosis being lung cancer (60–70%). Other causes include lymphoma, germ cell tumors, and breast cancer.

Although not considered to be an oncological emergency, SVCO can cause distressing symptoms and should be treated urgently. Lymphoma and small cell lung cancers causing SVCO are normally treated with chemotherapy, but in the usual case of NSCLC, RT is the treatment of choice, although intraluminal stents are increasingly being used, especially for patients who progress during or after their RT.

The radiation dose regimes employed for SVCO will depend on the underlying histology and the intent of treatment. Patients with lymphoma and germ cell tumors may be treated as part of a curative protocol, using radical doses of RT given in conventional daily fractions. Most patients with NSCLC will be treated with palliative intent although occasionally it may be appropriate to use a curative regime. Doses tend to be similar to those used for locally advanced NSCLC (see the section Lung Cancer), although some oncologists use larger than normal fractions for the initial few treatments if the patient is very symptomatic, to expedite response. Response rates between 40–90% (36,38,66) have been reported depending on underlying histology, treatment regime, and patient population.

Other lymph node masses that are causing pain or distress can be treated by short courses of palliative RT, usually 20–30 Gy in 5–10 fractions. Unsightly or painful lesions in the skin or subcutaneous tissue can be managed similarly. Response rates vary depending on the underlying histology but are probably in the order of 50–70%, although sometimes only a small reduction in the actual volume of the malignant mass occurs, but this can still lead to significant symptom relief.

Spinal Cord Compression

Spinal cord compression is one of relatively few oncological emergencies. Its prompt recognition, diagnosis, and treatment may avert neurological deterioration and prevent paralysis. Spinal cord compression is usually due to extension of vertebral metastases into the epidural space or occasionally to paravertebral tumors. It may also be the result of vertebral collapse, with bony fragments causing cord compression. Up to 90% of patients with vertebral metastases experience pain before any neurological changes. Any worsening of back pain in a patient known to have or be at risk for developing bone metastases should be assessed promptly. Unfortunately, patients frequently do not bring symptoms to the attention of their physician early enough. Many present hours after they have lost the use of their limbs, bladder, and/or bowel. If paraplegia has been present for more than 24–48 hours, it may be impossible to reverse the neurological damage. The most important predictor of neurological recovery is the ambulatory status at time of treatment of cord compression: 89% of patients who are ambulatory remain so after treatment, 53% of patients with paresis (weakness) become ambulant, but only 10% of patients with paraplegia (bilateral loss of leg power, i.e., bedridden) regain their mobility after treatment (67).

Palliative radiation is preferred over surgical decompression in patients who have very radiosensitive tumors (e.g., lymphoma, myeloma), have a limited life expectancy (days to a few weeks), and would find surgery to be too burdensome, have extensive vertebral or epidural metastasis where surgery stabilization would not be possible, present long after the loss of neurological function, and have continuing pain in the region of the cord compression, or are not candidates for surgery due to their debility or other contraindications. As with bone metastases, typical palliative treatment plans for spinal cord compression are 20 Gy in 5 fractions over 1 week or 30 Gy in 10 fractions over 2 weeks. The evidence for the role of RT in spinal cord compression has been reviewed recently (68). If complete paraplegia is present for a considerable time prior to presentation, there is little hope of neurological recovery, and palliative radiation may be reserved to manage pain in the future should it become a problem.

Treatment of the spinal cord in patients who have had previous spinal radiation presents a frequent clinical dilemma. If neurological status is threatened and surgery is not advisable, reirradiation may indeed be appropriate. Many radiation oncologists use smaller fraction size to minimize the risk of late complications, specifically radiation myelitis. The risk of radiation-induced paralysis cannot be completely dismissed but needs to be put into perspective of almost definite tumor-induced paralysis if treatment is withheld. In an already paraplegic patient, attention to maximum cord tolerance is not a concern. If pain is present, the patient can be treated with palliative radiation to the dose needed to control the pain without regard for the already damaged spinal cord.

WHAT AFTER RADIOTHERAPY?

Acute side effects are common and always self-limiting but as they usually occur after the treatment has finished, they can cause considerable anxiety if a patient is not warned to expect them. The common acute effects, their time course, and recommendations for management are shown in Table 49-7. In addition, many patients receiving RT will complain of fatigue during and after their course of treatment. The exact etiology of this is unknown but is probably multifactorial.

Site	Symptoms	Time course	Management
Skin	Erythema	Settles within 1 wk of completion of therapy	None, or 1% hydrocortisone for skin irritation if skin surface unbroken.
	Skin breakdown	Occurs only after higher dose XRT but if severe may last for several weeks	If only dry desquamation ("peeling"), no specific therapy except as above. If skin breaks down and begins to become ulcerated and weepy (moist desquamation), skin care required to prevent secondary infection.
Abdomen	Nausea and vomiting	May occur after first treatments and persist for several days after completion of therapy	Antiemetics (e.g., Gravol, Stemetil) used either as prophylaxis or as therapy for established emesis. Intractable cases may respond to steroids or ondansetron.
	Diarrhea	Occurs usually late in protracted course of XRT or after completion of short course of treatment	Prevention with low-fiber diet may be all that is required. Established diarrhea best treated with simple antidiarrheals (e.g., Lomotil, Imodium).
	Dysuria, frequency	As above	Exclude UTI by culturing MSU. If no bacterial infection, increase fluid intake, but symptoms may be difficult to control.
Head and neck	Painful inflammation of mouth, pharynx (mucositis)	Occurs during later stages of prolonged course of XRT, may persist for 1–2 wk after completion of therapy	Soft diet. Treat any secondary infection such as oral candidiasis. In severe cases, local anesthetic solution may be required.
Thorax	Dysphagia (esophagitis)	As above	Soft diet, analgesics. Patients may benefit from antacids to prevent reflux.
Head	Alopecia	Occurs over a few days after starting treatment	No specific therapy. Patients should be reassured that hair will regrow.

MSU, midstream urine; UTI, urinary tract infection; XRT, radiotherapy; XRT = ray radiotherapy.

TABLE 49-7. ACUTE SIDE EFFECTS OF RADIATION THERAPY

Late complications of RT, which occur months or years after treatment, are usually not relevant to many patients receiving palliative treatment. However, the radiation oncologist still needs to be mindful of the risks of inducing irreversible problems, such as myelitis, lung fibrosis, and renal failure, especially in patients who might have a long life expectancy, such as those with metastatic breast cancer.

Due to the low doses usually used, palliative RT is not necessarily a “once-only” treatment, unlike high-dose radical treatments. Therefore, if a patient treated for painful bony metastases develops recurrent pain in the irradiated area several months later, retreatment may be possible and should be discussed with the responsible radiation oncologist.

WHERE DO WE GO FROM HERE?

There is an urgent need for more clinical research in the area of palliative RT. Until now, the vast majority of clinical trial resources have been understandably channeled into curative treatment where end points, such as local tumor control, can easily be measured and compared. However, a substantial proportion of the radiation oncology workload—that done with noncurative intent—is based more on clinical experience, training, and resource utilization than on published data (8). A recent symposium concluded that “information on the palliative benefits of RT in terms of symptom management and quality of life is simply not yet available” (69). Nevertheless, there is increasing evidence that in many clinical situations single fractions of radiation are as effective as more protracted courses. Despite the obvious advantage to patients in terms of convenience and opportunity cost, in many radiation oncology centers, especially in the United States, there has been a reluctance to adopt this method of treatment, and it is unlikely that practice will change until large North American randomized trials demonstrate the same results as those from Britain and Europe. Accordingly, groups in both Canada and the United States have undertaken studies comparing the effects of single and multiple fractions for NSCLC and bone metastases.

Although it is important that more trials are performed, it is equally important that such trials are properly designed with reliable and valid end points. Guidelines for designing such trials have been published (70). Trials should be feasible in this population, the end points should be truly palliative, and the results should be representative of and applicable to clinical practice. It is essential that these principles be incorporated into future studies. Unfortunately, most of the trials discussed in this chapter are open to criticism because of the difficulty in measuring the palliative effect of radiation. Many of the end points used are subjective and response criteria are not well defined. Most studies use physician evaluation of responses as end points rather than self-assessments by the patients. Many of the more recent trials have incorporated validated instruments such as the McGill-Melzack pain score (71), analgesic intake scores, or linear analog self-assessment scales (35).

It is also fair to note that until recently, the radiation oncology profession has not demonstrated much interest in palliative RT research. However, it is now acknowledged that this is a fertile area for clinical studies, and several cancer centers are beginning to consider a programmatic approach. At the University of Toronto, programs designed not only to provide timely access to treatment for patients requiring palliative RT but also to enhance academic activity through education and research have been recently established (72,73). It is envisaged that a large proportion of the patients will be offered participation in clinical studies.

As more data become available, it is hoped that changes in practice may occur. For example, at present all patients at one center with bone metastases, irrespective of their primary diagnosis, histological subtype, or performance status, will tend to receive the same radiation prescription. However, within this heterogeneous group, there may be patients with factors that will make them more or less likely to respond to certain RT regimes. In addition, the effects of chemotherapy or other systemic treatments, such as bisphosphonates, may be synergistic with RT. It is hoped that future patients will have individualized palliative treatment plans, which will likely vary from single fraction radiation treatments in patients with limited life expectancy to longer and more complex combined modality approaches in those with more favorable characteristics.

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PALLIATIVE CHEMOTHERAPY

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Palliative chemotherapy is a term with many potential meanings. In its broadest sense, it refers to the use of anticancer medications in the treatment of an incurable malignancy. It is only one aspect of the wide spectrum of palliative care available for the patient with malignancy. The World Health Organization defines palliative care as “the active total care of patients whose disease is not responsive to curative treatment. Control of pain and other physical symptoms as well as psychological, social, and spiritual problems is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families” (1).

A myriad of cancer-related problems can affect any organ system and adversely affect overall quality of life (QOL). Health care providers intuitively realize that significant tumor responses to chemotherapy are usually associated with a decrease in malignancy-induced symptoms. The medical literature previously reported the effectiveness of palliative chemotherapy primarily in terms of tumor response rate, duration of response, and survival benefit; chemotherapy studies infrequently described palliation of symptoms or overall impact on QOL as an assessed treatment end point. Symptomatic improvement is now becoming a more important aspect in clinical trial evaluation and comprehensive cancer care. For example, a recent analysis of 300 patients treated with chemotherapy for metastatic breast cancer demonstrated that objective tumor response correlated with improvement of pain, mood, and shortness of breath. Constipation, lethargy, anorexia, and nausea also improved to a lesser degree, but there was no significant change in cough or insomnia (2). Improvement in symptoms may also occur without objective anticancer response to chemotherapy (3). In fact, it is estimated that 3000 articles describing cancer treatment effects on QOL will be published in 2002 (4). For the purpose of this discussion, palliative chemotherapy refers to the administration of medications to ameliorate the adverse signs and symptoms directly or indirectly caused by a malignancy that is incurable with the administration of chemotherapy. Excluded from our definition, however, are analgesics and psychotropic agents.

USUAL RATIONALE FOR CHEMOTHERAPY USE

Chemotherapy can be used as adjuvant, curative, or palliative treatment, depending on the type and stage of malignancy. When used in the latter two circumstances, its effect is usually described by response rate. Response rate primarily refers to objective measurements of changes in cancer size, sites of metastatic disease, and measurable serologic or other markers of tumor activity. Commonly used criteria for evaluation of solid tumor response to chemotherapy are shown in Table 50-1. Adjuvant chemotherapy refers to systemic treatment administered after all gross evidence of disease has been controlled by surgery or radiation therapy, but when the possibility of cancer recurrence is high. Adjuvant chemotherapy is given with the intent of completely eradicating any undetectable cancer cells that may be present. The benefit to toxicity ratio of adjuvant chemotherapy is extremely important. Most health care providers do not suggest very toxic or potentially lethal adjuvant chemotherapy if the likelihood of cancer recurrence is low and the percentage of patients likely to benefit is also low (i.e., residual cancer cells may not be killed with the treatment). In this instance, the treatment may harm more patients than it helps. Yet the individual with the cancer can have a very different perspective regarding this issue. Patients are often willing to undergo adjuvant therapies of prolonged duration and endure significant impairment in their QOL for a relatively small increase in the likelihood of cure (5). An additional benefit of adjuvant chemotherapy is the positive psychological effect of “doing something” to decrease the risk of cancer recurrence.

Definitions of overall response	
Response	**Definition**
Complete response	Complete resolution of all lesions (both target and nontarget) without new lesions
Partial response	Complete resolution of all target lesions and incomplete/stable response in nontarget lesions/sites without new lesions, OR Partial response of target lesions and nonprogression of nontarget lesions/sites without new lesions
Stable disease	Stable target lesions, nonprogression of nontarget lesions/sites without new lesions
Progressive disease	Progressive disease in target lesions, any response in nontarget lesions/sites, with or without new lesions, OR Any response in target lesions, progressive disease in nontarget lesions/sites, with or without new lesions, OR Any response in target lesions, any response in nontarget lesions/sites, and new lesions
Unknown	Response is not assessable, insufficient data reported

Adapted from Cancer Therapy Evaluation Program, 1998, April 30, Common Toxicity Criteria (CTC), Version 2.0 ctep.info.nih.gov/CTC3/ctc.htm, with permission.

TABLE 50-1. RESPONSE CRITERIA FOR SOLID TUMORS (EASTERN COOPERATIVE ONCOLOGY GROUP)

Chemotherapy can be palliative when used in conjunction with another anticancer therapy if it decreases treatment-related morbidity, even if it does not improve the chance of cure. For example, anal or laryngeal carcinoma can often be locally controlled or cured with aggressive surgery. This success, however, comes with significant morbidity— the need for colostomy or loss of voice. Organ function can be maintained for patients with these and other malignancies by combined chemotherapy and radiation therapy (6,7,8,9 and 10). It is anticipated that more malignancies will be treated with these organ-sparing treatments in the future.

As a primary treatment, chemotherapy may either be curative or “palliative” in instances in which there is no chance for cure. The goal of curative chemotherapy is to eradicate all cancer completely and to prevent its reoccurrence. Table 50-2 lists the malignancies for which chemotherapy has been shown to provide the possibility of cure in the nonadjuvant setting. These metastatic or locally unresectable cancers are considered to be very chemotherapyresponsive. Chemotherapy should be recommended in most circumstances for these cancers. Maintenance chemotherapy (that is, treatment continued for prolonged or indefinite periods of time after complete response is obtained) has been shown to be of no benefit for a number of chemotherapy-curable or highly chemosensitive cancers (testicular cancer, small cell lung cancer, ovarian cancer, lymphomas, and Hodgkin's disease).

Proven benefit of adjuvant chemotherapy	Possible curative primary or secondary chemotherapy for locally advanced or metastatic disease
Breast cancer	Acute lymphocytic leukemia
Cervical cancer	Acute myelocytic leukemia
Choriocarcinoma	Choriocarcinoma
Colon cancer	Germ cell/testicular cancers
Ewing's sarcoma	Hodgkin's disease
Germ cell tumors	Intermediate or high-grade non-Hodgkin's lymphomas
Lymphomas	Some predominantly pediatric tumors
Osteogenic sarcoma	Osteogenic sarcoma
Ovarian cancer	Rhabdomyosarcoma
Pediatric malignancies	Wilms tumor
Testicular cancer	Ewing's sarcoma
Small cell lung cancer	
Subtypes of high-grade carcinoma of unknown primary	

TABLE 50-2. CANCERS THAT ARE POTENTIALLY CURABLE WITH CHEMOTHERAPY

Unfortunately, the majority of metastatic malignancies in adults are not curable with chemotherapy. Even for the large number of patients with colon or breast cancer for whom adjuvant chemotherapy is recommended, treatment decreases the recurrence rate by only approximately one-third. Thus, many patients who experience recurrent disease after adjuvant treatment may also receive palliative chemotherapy.

PATIENT ACCEPTANCE OF THE NEED FOR CHEMOTHERAPY

After recovering from the initial shock of cancer diagnoses, patients appear to be quite willing to accept chemotherapy's side effects in an attempt to control the malignancy. In a study of 100 patients with cancer, Slevin reported the differences between patients' attitudes toward either mild or intensive chemotherapy. This information was compared to a similar survey of doctors, nurses, and a control group matched for age, sex, and occupation (11). Study participants were asked to consider various probabilities of cure, prolongation of life, and relief of symptoms necessary for them to accept toxicities associated with mild and aggressive treatments. Cancer patients were most likely to accept intensive and toxic treatments for an extremely small probability of cure, prolongation of life, or symptom relief. For example, 53% of patients with cancer would undergo a very toxic chemotherapy regimen for a 1% chance of cure, and 42% would accept the same regimen for a 3-month prolongation of life. Twenty percent of patient-appointed surrogate decision makers would accept the treatment for a 1% chance of cure, and the same percentage would accept it for a 3-month prolongation of life. The respective endorsement by medical oncologists was only 10% for each question (11). The control group was also less likely to accept the treatment-related side effects and wanted more potential benefit for any particular risk. Medical oncologists were more likely to accept aggressive treatments than general practitioners. Oncology nurses' scores fell between those of the generalists and the control group. Radiation oncologists were the least likely of any group to accept treatment. After 3 months of actual treatment, the same questionnaire was readministered to patients. Their responses were essentially unchanged. This important study indicates that individuals' attitudes change dramatically when they actually receive the diagnosis of cancer; when the situation is real, more risks are taken. Patients younger than 40 years of age are even more likely to undergo chemotherapy for extremely little predicted chance of symptomatic or longevity benefit (12).

CHEMOTHERAPY RESPONSIVENESS OF MALIGNANCIES

The likelihood of palliative chemotherapy benefit varies among cancer types. Malignancies with moderate to high sensitivity to chemotherapy are listed in Table 50-3. Anticipated chemotherapy response rates are in the 30–80% range. The primary goal of chemotherapy for these incurable, locally advanced or metastatic cancers is to achieve a partial or complete tumor response and to prolong diseasefree and overall survival.

Bladder cancer
Breast cancer
Cervical/endometrial cancer
Chronic lymphocytic leukemia
Chronic myelogenous leukemia
Colon cancer
Esophageal cancer
Head and neck cancer
Multiple myeloma
Non-Hodgkin's lymphoma (most subtypes)
Non–small cell lung cancer
Ovarian cancer
Prostate cancer (hormone therapy)

TABLE 50-3. METASTATIC AND INCURABLE CANCERS WITH MODERATE TO HIGH RESPONSE RATES (>30%) TO CONVENTIONAL CHEMOTHERAPY AND HORMONAL THERAPY

Metastatic or locally advanced cancers that have low expected response rates to chemotherapy are listed in Table 50-4. Partial responses to chemotherapy of less than 25%, usually of short duration, have been reported for these malignancies. Complete responses are extremely rare. The oncologist can recommend chemotherapy of limited proven benefit, investigational treatments, or nonchemotherapeutic palliative supportive care as reasonable alternatives for patients with these malignancies. Most cancer specialists have anecdotal experience of an occasional patient's unexpected excellent response in these chemotherapy-resistant cancers. One is cautioned not to base treatment of the average patient on the anecdotal (and at times inexplicable or coincidental) outcome of an individual patient.

Adrenal carcinoma
Adult sarcomas
Almost all malignancies in patients with poor performance status (Eastern Cooperative Oncology Group 3 or 4)—see text
Carcinoid tumor
Gastric cancer
Hepatoma/biliary cancers
Kidney cancer
Melanoma
Mesothelioma
Most previously treated cancers
Prostate cancer (chemotherapy)
Thyroid cancer

TABLE 50-4. INCURABLE CANCERS WITH LOW RESPONSE RATES TO CHEMOTHERAPY (<30%)

Some chemotherapeutic agents have received U.S. Food and Drug Administration (FDA) approval primarily because they have improved QOL. A number of treatment studies report decreased pain or other symptomatic improvement induced by chemotherapy, despite little or no objective tumor response (13,14,15,16 and 17). Hypotheses to explain these phenomena include alteration in the local milieu of the neoplasm or the inhibition of production of circulating cytokines and neurotransmitters responsible for many adverse symptoms associated with malignancies (18,19 and 20). Changes in growth factor production could result in tumor growth inhibition, as opposed to tumor shrinkage. Decreased inflammatory responses induced by many chemotherapeutic drugs or antikinins have led to their widespread use in rheumatologic diseases (21,22). Similar local environment alterations may occur at tumor sites with a decrease in tumor-associated symptoms without necessarily influencing tumor size.

THE PHYSICIAN'S IMPACT ON TREATMENT CHOICES

The physician has considerable influence in the patient's decision about starting or continuing chemotherapy. Although the majority of adult cancer patients in one report (N = 439) wanted “all” information to be given, only 69% wanted to participate in the therapeutic decision making. Twenty-five percent wanted the physician to make all of the decisions. This latter group comprised predominantly older and sicker men (23). Although patients tend to accept their physicians' advice, this is not universal. A better-informed and educated patient or a patient who believes that his physician is ambivalent about a recommendation is more likely to decide independently (24).

Oncologists should not feel obligated to offer chemotherapy to every patient with malignancy. A group of patients for whom the predicted toxicity of treatment should preclude consideration of chemotherapy can be defined (see the section Prognostic Factors). Other patients may fall into a gray zone in which the benefit to toxicity ratio of treatment is less clear.

The practice of giving subtherapeutic doses of chemotherapy primarily to prevent patients from believing their cases are hopeless is strongly discouraged. This is more likely to reflect the physician's discomfort in dealing with a terminally ill patient than it is to address the patient's psychological needs. A more compassionate and ethical approach is to review the medical situation with the patient and family and to provide them with an informed assessment of possible treatment choices. Often this will include nonchemotherapy palliative care. This is especially true near the end of life. Patient and family desires for open communication and participation in decision making, which may be tempered by cultural differences, must be considered in these discussions.

Investigational studies of newer chemotherapy or palliative treatments are considerations when no proven beneficial anticancer treatment exists. The patient and family should understand that unproven investigational treatment may cause more harm than good. Patients and families may mistakenly believe that “no chemotherapy” means “no need for the physician to follow and treat the patient” or “nothing more can be done.” Palliative care should be offered as a positive intervention, rather than just the absence of chemotherapy. Future visits should be scheduled with the physician who is supervising the patient's care. Visits should be at intervals that meet the physical and psychological needs of the patient and family. Even when it seems likely that the patient will be too sick to keep any more appointments, they should be scheduled nonetheless. Such scheduling provides a message of ongoing concern for the welfare of the patient and caregivers.

DISCUSSING PALLIATIVE CHEMOTHERAPY WITH PATIENTS

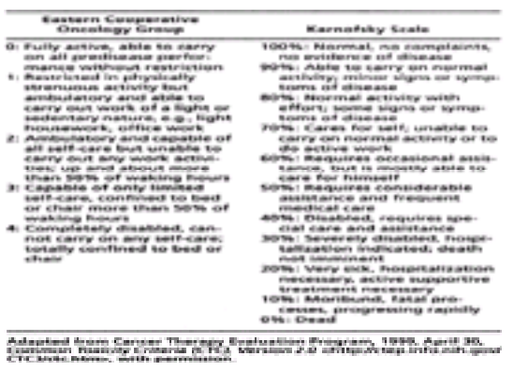
Patients and families often request statistics regarding the likelihood of tumor response, expected duration of response, possible treatment-related toxicities, and average survival prolongation that may occur with chemotherapy. This information may have significant impact on the decision to accept a recommended trial of chemotherapy. In addition to giving an honest reply, the physician should respond to these inquiries by trying to learn if there are specific factors leading to the question. What questions and decisions need to be addressed in the patient's or family's lives? Is there a contemplated retirement, a reunion, a special upcoming event, or significant unfinished business that must be completed? Are there fears about dying or spiritual issues that need interventions from other supportive caregivers?

Patients and families often misconstrue a survival estimate based on published or personal experiences as a precise number to live or die by. For example, a physician statement that the median survival is 6 months frequently leads to a 6-month survival time becoming firmly entrenched in the minds of patient and family. Similarly, an expected “20% response rate to treatment” for a published cohort of patients may be misconstrued by the patient to mean that he specifically has a 20% chance of responding to the same treatment. The patient must be informed that statistics refer to groups of patients and not individuals. Oftentimes, patients or their families insist on a numerical answer concerning therapeutic efficacy or expected longevity. They may honestly be informed with such phrases as, “I expect the time would more likely be measured in weeks than in months,” or “There is a reported response rate of 60%, which lasts on average for 4 months.” This is an opportunity to discuss possible scenarios and alternatives to the question, “What if a response does not occur?” Although these replies are not very precise—indeed, it is very difficult for a reply to these questions to be both honest and precise—they at least give the patients information to correct gross misconceptions about their prognoses. Although false hope should be avoided, it is possible to have these difficult discussions and still impart hope for comfort, maintenance of functionality for as long as possible, and finally, a death without uncontrolled pain or loss of dignity. Also important is the reassurance that the physician will continue to care for the patient and family, even if chemotherapy is no longer used (25).

When patients and their families are provided with the best possible prognostic information, decisions frequently differ from those made when less information is imparted. Patients with metastatic colon and lung cancer who believed that they had a significant chance of dying within 6 months were less likely to choose a possible life-extending therapy over comfort care (26). When informed that the likelihood of 6-month survival was 90, 75, 50, 25, or 10%, the likelihood that the patient would choose a lifeextending therapy was decreased to 51, 29, 29, 31, and 21%, respectively. In this study, patients, as compared to their physicians, more commonly overestimated their chance of surviving 6 months. For example, whereas 50% of physicians believed that a patient group would have a 6-month survival, only 12.5% of patient members of that group thought that they would survive 6 months or less. Physician estimates of prognosis were more accurate than the patient's own estimates, as evidenced by the fact that only 45% of the patient group was alive at 6 months. If chemotherapy is chosen by mutual agreement between the patient and physician, the attitude should be that all that is necessary will be done to assure that the particular patient will benefit from the treatment, even if the response rate is reported to be relatively low. This optimistic approach after a realistic discussion is appropriate and of great psychological benefit to the patient and the family, as well as the physician and other members of the health care team.

PROGNOSTIC FACTORS

A composite of patient and disease-related factors will help determine if chemotherapy is a reasonable treatment option. The single most important factor (other than tumor type) that determines possible benefit to toxicity ratio of chemotherapy is the performance status (PS) or activity level of the patient. Two measures used to quantitate this are the Eastern Cooperative Oncology Group (ECOG) and Karnofsky scales (Table 50-5). These two performance status scales have been compared in lung cancer, and in at least that setting, the ECOG scale has a somewhat better prognostic capability (27). Regardless of the cause of debility (malignancy or other comorbid medical illness), a severely weakened patient with a restricted PS (ECOG 3 or 4; Karnofsky <50%) is more likely to experience excessive toxicities from chemotherapy than a beneficial response. Exceptions occur predominantly when the malignancy causing the severe debility is exquisitely chemotherapy sensitive (28,29).



Eastern Cooperative Oncology Group	Karnofsky Scale
0: Fully active, able to carry on all predisease performance without restriction	100%: Normal, no complaints, no evidence of disease
1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work	90%: Able to carry on normal activity; minor signs or symptoms of disease 80%: Normal activity with effort; some signs or symptoms of disease
2: Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours	70%: Cares for self; unable to carry on normal activity or to do active work 60%: Requires occasional assistance, but is mostly able to care for himself
3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	50%: Requires considerable assistance and frequent medical care
4: Completely disabled, cannot carry on any self-care; totally confined to bed or chair	40%: Disabled, requires special care and assistance 30%: Severely disabled, hospitalization indicated; death not imminent 20%: Very sick, hospitalization necessary, active supportive treatment necessary 10%: Moribund, fatal processes, progressing rapidly 0%: Dead

Adapted from Cancer Therapy Evaluation Program, 1999, April 30, Common Toxicity Criteria (CTC) Version 2.0 http://ctep.info.nih.gov/CTC3Hp.htm, with permission.

TABLE 50-5. EASTERN COOPERATIVE ONCOLOGY GROUP AND KARNOFSKY PERFORMANCE STATUS SCALES

The sites of metastatic spread may allow better, but not totally accurate, predictions of the potential initial response to chemotherapy as well as overall prognosis. This varies for different tumor types (5). For example, breast cancer metastatic to the skin, bone, and lymph nodes is usually more responsive to chemotherapy than when liver or pulmonary lymphangitic metastases are present. Chemotherapy “sanctuary sites,” such as the brain and other central nervous system structures, are usually least responsive to systemic cytotoxic treatments.

Numerous other poor prognostic features exist for specific malignancies. Data are increasingly available to support genetic aberrations and histochemical markers as predictive of short- and long-term prognosis for malignancies, as well as the likelihood of response to chemotherapy (30,31 and 32). Patients whose cancers are refractory to ongoing chemotherapy are less likely to respond to second or subsequent chemotherapy treatments. Similarly, cancers that have recurred within 6 months of cessation of chemotherapy are less likely to respond to retreatment with the same chemotherapy than are those that recur after a longer disease-free period.

DOES AGE INFLUENCE THE DECISION TO TREAT OR ACCEPT CHEMOTHERAPY?

Pharmacokinetics change with the patient's age secondary to alterations in drug absorption, distribution, metabolism, and excretion (33,34). However, advanced age is reportedly not a prognostic factor in the response to chemotherapy, as long as there are no significant comorbid medical problems (35,36 and 37). There are differences in elderly patients' tolerances and responses to chemotherapeutic agents. Patients with colorectal cancer who were older than 70 years of age had greater 5-fluorouracil (5-FU) induced mucositis than did their younger counterparts, but response and survival benefits were similar as long as their initial PS was good (38). Specific cancer molecular characteristics may be different in elderly patients (39). They may have a higher prevalence of neoplastic cells with multidrug resistance, as well as ageassociated variances in tumor-associated enzymes and even in tumor kinetics. Polypharmacy and possible adverse drug interactions may occur with increased frequency in the elderly. In one report, 58% of cancer patients older than 70 used more than four other medications, 22% more than seven, and a remarkable 7% were using more than ten (40).

Some oncologists exclude older patients from chemotherapy treatments solely because of age and presumed risk of severe treatment-related toxicity (40). Adjuvant

chemotherapy is not offered as often to very elderly patients (older than 75 years of age) with colon cancer compared to younger elderly patients (younger than 70 years of age) (41,42). Studies of adjuvant therapies for breast cancer suggest that women older than 65 are less likely to have breast conserving surgery, be referred to medical oncologists, and be offered adjuvant treatments (43,44,45 and 46). The aged are less likely to receive anticancer-directed therapies for many other different stages and types of cancer, as well (39).

Yet many studies suggest that the elderly tolerate at least some treatments as well as younger patients do (38,47,48,49 and 50). Despite the apparent bias against treating the very elderly with tamoxifen citrate, they tolerate its side effects better than younger patients (18). Paradoxically, the elderly may be more able to cope with some of the inconveniences and life-style changes inherent in receiving chemotherapy. They have reported less discomfort with procedures, less anxiety in medical situations, and less difficulty in adjustments in the work environment than their younger counterparts. (51).

Older patients agree as readily as younger patients to undergo trials of aggressive chemotherapy for curative or palliative purposes; however, older patients appear less willing to trade significant toxicity for increased survival time (12,52). Older patients are more likely than their younger counterparts to shift to a milder, less toxic treatment, even if survival is predicted to be shorter.

Individuals of any age who are residing in the same dwelling as their children more commonly accept aggressive treatments (53). Patients residing with their spouse do not as predictably opt for this same aggressive treatment. Patients who have previously received chemotherapy more readily accept aggressive and potentially more toxic forms of chemotherapy than treatment-naive individuals (52). This finding lends empirical support to the possibility that actual experience with chemotherapy may not be as difficult as patients' expectations of the difficulties. In one report, individual life goals and the sacrifices one is willing to accept were unpredictable across socioeconomic, religious, and cultural backgrounds (54). “Make no assumptions” remains very worthwhile advice.

QUALITY OF LIFE

QOL measurements were infrequently recorded or reported during the first four decades of modern chemotherapy trials. QOL measurements refer to a quantitative evaluation of numerous qualitative parameters that are instrumental in day-to-day enjoyment of life. As stated previously, QOL assessments are increasingly reported as independently assessed variables in clinical trials. Multiple QOL scales of varying complexity have been developed. Examples of parameters measured include pain and pain relief, fatigue, malaise, psychological distress, nausea and vomiting, physical functioning, treatment-related symptoms and toxic effects, body image, sexual functioning, memory, concentration, economic impact of the disease, and global QOL (55,56,57 and 58). These QOL inventories may be used in conjunction with the more commonly used measurements of chemotherapy-induced toxicities to better assess overall patient tolerance to the drug regimen administered (57,59,60,61 and 62).

A patient's QOL is a subjective parameter that can be misjudged by the health care provider and a patientappointed surrogate (61). Malignancy or treatment-induced debilities may be better tolerated by individuals with previous disabilities. Younger, more active patients may have significant difficulties with a functional compromise. The loss of hair for one patient may be more psychologically debilitating than a decrease in mobility for another. Each patient and situation is unique, and QOL is an experience that can change dramatically over time.

At times, logistic QOL issues as opposed to health-related QOL issues become quite important in the patient's decision to accept a chemotherapy regimen. Length of treatment, impact on family life, or travel distance to the treatment center may weigh more heavily on decisions for chemotherapy than do actual drug-related toxicities (62). A common misconception is that if a chemotherapy regimen is inducing a beneficial tumor response, then toxicities may be more tolerable to the patient. A study of 99 patients reported little difference in side effect ranking between those patients who thought they were getting better and those who thought that they were the same or worse (63). Interestingly, in this same study, nonphysical side effects of treatment, such as the inconvenience of coming for appointments, time spent in the treatment facility, difficulty parking at the clinic, and problems that treatment created for the patient's family or work environment, were frequently listed as more bothersome than physical side effects such as vomiting, nausea, hair loss, or fatigue. More research is required to define these complex QOL issues accurately. It appears prudent for the health care team not to judge the patient's level of debility or QOL.

An assumption by the health care team that a marked improvement in QOL with a slight decrease in overall survival would be in the cancer patient's best interest may be incorrect. In a study of health values of the seriously ill, patients and their self-designated medical decision-making surrogates were independently interviewed (61). The patients had a variety of chronic debilitating diseases with an anticipated median 6-month mortality rate of 50%. All patients had significant disease-related debility. Patients were evaluated for time trade-off—if they could live 1 year at their current level of function and health, how much time would they trade for a shorter survival in excellent health? Approximately one-third of the patients would not give up any time at their present level of debility in exchange for even 1 week less of life but in excellent health. At the other extreme, 9% preferred living 2 weeks or less in excellent health to 1 year in their current state of health. Only 2% of patients described their current health as no better than death. On average, only 3.2 months would be returned for the prospect of an absolutely healthy life instead of 1 year at their current state of disability. In general, patients rated their current state of health as better than did their designated surrogates. If surrogates were to make decisions for patients, those surrogates were more likely to give up survival time for improved health. This study emphasizes that patients' health values cannot be predicted accurately by others. In general, patients accept great sacrifices to live the maximum amount of time. When sequential interviews with the same patient were possible, health values increased with time—the longer the patient survived, the less likely he was to trade time alive for better health.

PALLIATIVE CHEMOTHERAPY—SPECIFIC EXAMPLES

Prostate Cancer

Which patients benefit from palliative chemotherapy, and when should it be recommended? Metastatic prostate cancer serves as an example of some of the difficulties in clinical decision making. It is usually a disease of older men, many of whom have significant comorbidities. Assessing treatment response is often difficult because most patients have metastases primarily in bone, a site in which a decrease in tumor size is difficult to prove. Reductions of more than 50% in prostate specific antigen levels correlate with improved survival and symptom control; smaller declines have not been shown to be clinically meaningful (64).

Despite these difficulties, well-designed phase III studies have shown a benefit of palliative chemotherapy in patients with hormone-refractory prostate cancer. Glucocorticoids used as a single agent are somewhat useful (65,66). Mitoxantrone hydrochloride plus hydrocortisone or prednisone yielded modest improvements in QOL measurements compared to glucocorticoid alone (67,68). Suramin with or without hydrocortisone (69) demonstrated pain improvement and delay in disease progression but with no benefit in overall QOL.

Colon Cancer

Treatment standards are rapidly evolving for patients with metastatic and recurrent colon cancer. Until recently, the combination of 5-FU plus leucovorin has been the standard treatment for this disease. Two randomized studies address the usefulness of irinotecan in patients who present with metastases or have progressive disease after standard therapy. Compared to infusional 5-FU irinotecan prolonged survival, but the relative impact on QOL was not significant (70). When irinotecan was compared to best supportive care (BSC) alone in this population, a survival benefit, as well as improvement in most measures of QOL, was observed (71). In a randomized trial in previously untreated patients, irinotecan alone was compared to 5-FU plus leucovorin and to the combination of all three agents. The triple-agent therapy significantly improved progression-free and overall survival without adversely affecting overall QOL (72,73). Preliminary data suggest that capecitabine, an orally administered fluoropyrimidine used in the treatment of recurrent colon cancer, provides a higher response rate with a more favorable toxicity profile than does 5-FU plus leucovorin (74,75).

Non–Small Cell Lung Cancer

There have been four prospectively randomized trials that compare single-agent chemotherapy versus BSC in previously untreated patients with advanced non–small cell lung cancer (NSCLC). Patients older than 70 years of age with good PS treated with vinorelbine tartrate scored better than controls on QOL function assessment scales (76). They reported fewer cancer-related symptoms, despite experiencing worse toxicity-related symptoms; there was a modest survival advantage for patients receiving vinorelbine tartrate. A large study comparing gemcitabine plus BSC versus BSC alone used QOL measurements as its primary end points (77). The gemcitabine-treated patients had significantly better QOL and reduced disease-related symptoms compared with those receiving BSC alone. The QOL improvement lasted greater than 4 weeks in 22% of the gemcitabine plus BSC patients, but in only 9% of the BSC patients; no survival advantage was noted.

Taxanes currently available for use in the United States, docetaxel and paclitaxel, have been tested in prospectively randomized trials of NSCLC patients and compared with BSC alone (78,79). The addition of paclitaxel to BSC improved median survival (by approximately 2 months), time to disease progression, and some aspects of QOL. In a similar trial, docetaxel plus BSC significantly improved clinical symptoms and had a favorable impact on overall survival, despite the low response rate of only 13%. QOL descriptors favored docetaxel, with significant improvement demonstrated for pain, dyspnea, and emotional functioning. Docetaxel has also been shown to be of palliative benefit as a second-line agent to treat NSCLC patients previously treated with platinum-based chemotherapy (79).

Breast Cancer

In the initial treatment of locally advanced or metastatic breast cancer, the benefits of hormonal therapy and chemotherapy on overall survival and QOL are proven (2,80). Less obvious are the benefits of such therapies when used after first-line therapies fail.

Because their toxicity is generally low and thus their therapeutic index is high, it is not surprising that secondline hormonal therapy can improve QOL in breast cancer patients. A study of 177 women whose breast cancer progressed on tamoxifen citrate found that responses to subsequent hormonal therapy correlated well with sustained or improved QOL (81).

The data concerning the palliative benefit of chemotherapy for breast cancer progressing after initial chemotherapy are less compelling. In 1999, Campora et al. noted that the median survival for metastatic breast cancer had not varied for 50 years, remaining in the range of 2.0–3.5 years (82). In their retrospective analysis of treatments in the pretaxane era, the likelihood of benefit of chemotherapy after failure of first-line anthracycline-containing therapy was never more than 15%.

The availability of the taxanes has changed the approach to patients with recurrent breast cancer refractory to anthracycline chemotherapy. Docetaxel has been compared to mitomycin plus vinblastine sulfate; it produces a longer time to progression, greater overall survival, and a similar impact on QOL (83). Studies comparing its palliative benefits to those of vinorelbine tartrate give mixed results. One study found that both taxanes, paclitaxil and docetaxil, were similar in benefit to vinorelbine tartrate, with the latter being less expensive (84). Another study found that docetaxel was better than paclitaxel and vinorelbine tartrate, both in alleviation of malignancy-related symptoms and cost-effectiveness (85).

Several approaches to overcome the limitations of palliative chemotherapy for recurrent breast cancer have been tried. The first approach is to use single agents sequentially rather than in combination. In a randomized trial, patients treated with single-agent epirubicin hydrochloride followed by single-agent mitomycin had similar survival but less treatment-related toxicity and better QOL, as compared with those treated with cyclophosphamide plus epirubicin hydrochloride plus fluorouracil followed by the combination of mitomycin plus vinblastine sulfate (86).

Another way to reduce treatment toxicity is to discontinue treatment after remission is achieved. This method seems less promising than the use of sequential single agents. A prospective randomized trial compared treating women with recurrent breast cancer with cyclophosphamide plus methotrexate plus 5-FU plus prednisone continuously versus the same drugs given for three cycles and then repeated for another three cycles on evidence of disease progression (87). QOL improved for both groups during the initial three cycles of chemotherapy; after that, intermittent therapy was associated with worse scores for physical wellbeing, mood, appetite, and QOL.

Finally, a herald of future therapies is the use of trastuzumab, a monoclonal antibody approved to treat metastatic breast cancer. It is targeted against HER2, a marker that is up-regulated in a minority of cases of breast cancer. In a phase III study, the effects of trastuzumab plus limited chemotherapy were compared with those of chemotherapy alone. Although the monoclonal antibody did not improve QOL scores, at least in the doses and schedules used in these studies, trastuzumab was not associated with worsening of health-related QOL (88). Another study showed a significant survival advantage from adding trastuzumab to standard chemotherapy of women whose metastatic breast cancer overexpresses HER2 (89).

Pancreatic Cancer

Finally, no discussion of palliative chemotherapy would be complete without a mention of the use of gemcitabine hydrochloride in the treatment of advanced pancreas cancer (90,91). It is important for historical as well as clinical reasons. In 1985, a three-way randomized trial had proven that neither 5-FU plus doxorubicin nor that combination plus mitomycin was better than 5-FU alone in the treatment of metastatic pancreas cancer (92). Although 5-FU remained the most commonly used treatment of advanced pancreas cancer, there were no studies showing that it prolonged survival or improved QOL. When the FDA approved gemcitabine hydrochloride for this indication in May 1996, it ushered in a new era in medical oncology. Gemcitabine hydrochloride was the first chemotherapy drug cleared for marketing by the FDA based on a unique clinical end point assessing the effect of the drug on measured disease-related symptoms; the end point is called *clinical benefit response*. No longer would response rate or survival be the only criteria of approval for chemotherapy; the importance of QOL as a legitimate end point in cancer chemotherapy could no longer be ignored.

WHEN TO INITIATE PALLIATIVE CHEMOTHERAPY

When curative therapy is not a realistic goal, as is the case in most adult metastatic malignancies, then multiple factors must be weighed regarding the time to initiate systemic anticancer therapy. The goal of palliative chemotherapy must be to relieve or prevent tumor-induced symptoms or to prolong survival.

Because any symptom caused directly or indirectly by the neoplasm can potentially be ameliorated by an effective chemotherapy regimen, patients who are symptomatic from malignancy or are expected to become symptomatic soon should be considered for treatment. Chemotherapy as the sole treatment has been used effectively to palliate emergencies such as superior vena cava syndrome, epidural spinal cord compression, or airway obstruction due to chemosensitive tumors (93,94,95 and 96). When these emergencies occur in patients whose tumors are more resistant to chemotherapy, they are more appropriately managed with a local treatment such as radiotherapy or surgery.

A difficult choice is whether to delay noncurative chemotherapy for the asymptomatic patient with low volume of disease in nonvital areas, because some tumor types may display indolent growth. These patients may experience no signs or symptoms from their malignancy for prolonged periods of time. In these circumstances, especially for cancers with low expected response rates to chemotherapy, the benefit to toxicity ratio of therapy may be more heavily weighted toward the toxicity side. Forestalling initial cytotoxic treatment then becomes an attractive alternative. Treatment can be withheld with close monitoring of the patient and initiated once symptomatic progression is evident or anticipated to occur soon.

A primary concern for this “watch and wait” approach is that a patient can move from “too well to treat” to “too sick to treat” quickly and unexpectedly. This is especially problematic if the patient desires a trial of chemotherapy. Treatment could be withheld, and then unexpected severe problems may prevent the patient from receiving chemotherapy, thus missing the elusive “window of opportunity.” The possibility also exists that a malignancy may demonstrate a decreased response to treatment with increased tumor size (97,98). Delay of chemotherapy theoretically allows for the potential development of more chemotherapy-resistant cells.

Prospective trials for most types of incurable malignancies do not permit a definite recommendation regarding whether to initiate treatment at the time of diagnosis or “watch and wait” for the asymptomatic patient. A candid discussion of options is essential in making this decision. Some patients would be psychologically distressed with a delay of therapy. If there are objective parameters to follow for tumor response to treatment, two to three courses of treatment with reevaluation for response is a reasonable approach. Treatment could continue for regressive disease or be discontinued or changed for tumor progression. If toxicities from treatment are severe, attenuation, change, or cessation of treatment are alternatives to consider. The case of stable disease is more problematic. Slowly growing tumors refractory to chemotherapy may not demonstrate apparent growth until after many months of treatments. It may be impossible to judge if the cancer is just displaying a slow growth phase or if the treatment is keeping the disease “in check.” This is especially true with the recently developed cytostatic agents that can be given individually or in combination with cytotoxic agents (99). One must be cautious when attributing stable disease to chemotherapy “response,” but clearly a cancer that is not growing or causing difficulties is better than one that is. If the treatment is not causing significant side effects, it would be reasonable to discuss with the patient the possibility of continuing the treatment until the time of disease progression versus discontinuing treatment and resuming it at the time of progression.

The decision to treat the asymptomatic patient becomes even more difficult if there is no disease that can be followed for response to treatment and the response rate to chemotherapy is relatively low. Prospective follow-up studies from baseline can then only report on disease progression. A “watch and wait” policy for the patient without symptoms or followable disease, with reservation of treatment until the disease becomes measurable or symptomatic, is one option. The other choice is a finite number of chemotherapy cycles (4–8 months), unless previous clinical trials have determined optimal duration of treatment.

SUMMARY

It is possible to develop an overall palliative chemotherapy approach to the patient with an incurable malignancy. Newer and more effective regimens that have fewer or milder toxicities and higher responses are increasingly available. Paradoxically, the most reasonable patient group for inclusion in clinical trials is comprised of those patients who present in the best health. This would include patients with ECOG PS 0–2, no cancer-related symptoms (e.g., weight loss), and few, if any, other significant comorbid medical problems. Unfortunately, this “ideal patient group” is often underrepresented in patients presenting with metastatic incurable malignancies. Patients with minimal comorbid conditions and malignancies of moderate to high sensitivity to chemotherapy should be offered an initial trial of treatment. Treatments could continue or be changed dependent on response, published data, and clinical situation. The more problematic situations are the cases with a relatively low response rate (<25%) to chemotherapy. If access to clinical trial protocols is available, they may be recommended. If trials are refused or not available, a limited duration of chemotherapy can be given. If a partial or complete response is observed and the patient's PS and QOL are stable or improving, then continuation of

treatment to best response, one or two cycles beyond best response, or even for very extended times would be reasonable alternatives. If the cancer is responding to treatment but the patient is doing poorly, with decreasing PS or QOL, the goals of these noncurative therapies must be reassessed and discussed with the patient. Stepwise attenuation of doses, prolonged intervals between chemotherapy cycles, different chemotherapy regimens, and chemotherapy-free rest and recovery intervals are alternatives to be considered. Included in the discussion of treatment options, especially with this group of patients, is the possibility of no further chemotherapy and provision of aggressive and state-of-the-art symptom management. The patient should be reassured of the physician's commitment to continued care. The physician must allay fears by reassuring both patient and family that although specific treatments may be discontinued, the patient will never be abandoned.

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PALLIATIVE SURGERY

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It is projected that in the year 2002 there will be 1,284,900 new cases of cancer diagnosed in the United States, and 555,500 cancer-related deaths (1). Surgery continues to be the mainstay of curative treatment for most solid tumors. However, surgeons continue to see a large number of patients in their practices that either present with advanced-stage incurable malignancy or, in follow-up after primary surgical treatment, present with new or recurrent cancer-related surgical problems.

The term *palliative surgery* is not clearly defined. In the broadest oncologic sense, palliative surgery refers to surgery that is by nature noncurative. A palliative resection is generally defined as the surgical extirpation of a primary tumor without removal of all grossly identifiable disease or in the presence of positive margins. Palliative surgery also increasingly encompasses surgical procedures that are aimed primarily at the treatment of symptoms or complications associated with a tumor or its treatment. Regardless of whether the palliative nature of a surgical procedure is determined preoperatively or postoperatively, the primary aim should be the relief of symptoms, with preservation or improvement in the quality of life.

Palliative care of the cancer patient has received little attention and emphasis in the surgical literature. Miner and colleagues reviewed the literature on surgical palliation between 1990 and 1996 and noted a total of only 348 citations (2). Among these entries, consideration of pain control and quality of life were reported in only 12% and 17%, respectively, whereas consideration of morbidity and mortality and survival were reported in 61% and 64%, respectively. Moreover, utilization quality of life and symptom assessment tools for surgical patients is not infrequently flawed (2a). Until recently, comprehensive palliative care of the cancer patient has received little attention or emphasis in the surgical literature, much as the topics around end-of-life care have been largely neglected in standard surgical texts (2b,2c). The need to refocus surgeons' attention on palliative care has been highlighted by endorsement from the American College of Surgeons (3) and by the appearance of a growing number of surgical publications dealing with its many facets (3a,3b). It is also well recognized that graduate and postgraduate training in palliative care is spotty (4).

A recent survey of 420 responding members (24%) of the Society of Surgical Oncology was conducted to test the definition of palliative surgery, assess the extent of its use, and evaluate the attitudes and goals of surgeons regarding palliative surgery (5). Forty-eight percent reported having received no palliative care training in medical school, 30% reported having received no training in either residency or fellowship training in the area of palliative care, and 24% had received no continuing education in palliative care. In contrast, respondents reported an average of 21% of their cancer surgeries as palliative. The definition of palliative surgery was best defined preoperatively by 43% of respondents, based on postoperative factors by 27%, and based on patient prognosis by 30%. The most important finding in this survey was that quality of life parameters (e.g., symptom and pain relief) were identified as the most important goals in palliative surgery, with increased survival being the least important. This report emphasizes the need for prospective studies of palliative surgery that focus on quality of life measures.

Palliative care of a cancer patient involves the total care of a patient whose disease is not responsive to curative or life-prolonging therapy. The goal is to provide the best quality of life for the patient and family (5a). While this may focus on relief of pain and distressing symptoms, it also calls on the surgeon to function as part of an interdisciplinary team, addressing the multitude of physical, psychosocial, and spiritual issues facing patients and their families. Surgical intervention may be required at any time along the continuum from onset of symptoms to death. The test of a surgical procedure therefore in providing palliation is not whether there has been any effect on the underlying disease, but whether it leads to an improvement in the quality of life of the patient.

The decision to intervene surgically to achieve palliation is often a complex one, requiring superior judgment. It requires identification of the goals of care, so that the plan of course— which may or may not include surgical intervention— becomes a reasonable means to those ends. This decision requires consideration of procedure-related morbidity and mortality, which must be weighed against the morbidity of nonintervention and the anticipated survival time. The ultimate mode of death with or without surgical intervention must also be considered. The end point of intervention must always be either the relief or the prevention of symptoms. Cost analysis is also a necessity in this era of cost containment. Consideration should be given not only to the direct costs of intervention, but also to costs related to general care and the management of complications, both with and without intervention. It behooves the surgeon to avoid inappropriate interventions, particularly those that prolong the dying process. This unfortunate situation is likely to occur due to a lack of education and training in palliative care, and may be further accentuated by prevailing attitudes in society and in the medical profession that defy death and strive to prolong life.

An important component of the decision-making process in surgical palliation, particularly in the terminal phase of illness, is the estimated survival time. Physicians, however, are notoriously poor prognosticators. Christakis et al. prospectively analyzed the ability of 343 doctors to estimate survival time in 468 terminally ill hospice patients, 65% of whom had cancer (5b). They noted that predictions of survival were overoptimistic in 63% of cases, and that the physicians overall overestimated survival time by a factor of 5.3. The tendency of doctors to make prognostic errors was lower among experienced doctors. This undue optimism about survival prospects may have negative implications for patient care, including an overenthusiasm for surgical intervention and a tendency for late referral to hospice care. Models of prognostic indices have been developed for clinical research that have been shown to predict short-term survival reasonably well. In practice, however, there are general guidelines for determining prognosis in advanced malignant disease that surgeons need to be familiar with. The functional status of the patient is the single most important predictive factor (Table 51-1).

	Median survival time
Performance status (Karnofsky ≤50 or Eastern Cooperative Oncology Group ≥3)	3 mo
Chemotherapy related	
Disease progression after 2 cycles of chemotherapy	<6 mo
Untreated metastatic solid cancers, acute leukemia, high-grade lymphomas	<6 mo
Tumor related	
Hypercalcemia (except newly diagnosed myeloma or breast cancer)	8 wk
Pericardial effusion	8 wk
Leptomeningeal carcinomatosis	8–12 wk
Multiple brain metastases	
With radiation	6 mo
Without radiation	1–2 mo
Malignant ascites or pleural effusion	<6 mo
Abdominal carcinomatosis	3–6 mo

TABLE 51-1. GENERAL GUIDELINES FOR DETERMINING PROGNOSIS IN ADVANCED MALIGNANT DISEASE

The other key element of the decision-making process in surgical palliation is the extent of the surgical procedure. The range of surgical procedures is outlined in Table 51-2. Supportive procedures (e.g., insertion of a vascular access device) are generally well tolerated, particularly those that are performed under local anesthetic. On the other end of the spectrum is palliative resection, which may be associated with high morbidity and mortality. Patients presenting with more advanced disease or with residual disease at completion of surgery are not anticipated to do as well postoperatively compared to patients who undergo curative resection. Patients undergoing palliative procedures generally have poorer performance status. With postoperative mortality rates of 10% and morbidity rates as high as 25% commonly

reported in the palliative surgical literature, it is imperative that adequate measures of palliation be defined. It is essential that the morbidity of the surgical procedure should not exceed that of the disease. This is why it is imperative that quality of life outcomes be evaluated by improved research methods.

Palliative (intervention as treatment)
Drainage of effusions
Ascites
Pleural
Pericardial
Obstruction
Respiratory
Gastrointestinal
Genitourinary
Vascular
Tumor resection
Toilet procedure
Bleeding
Fistulas
Supportive (multidisciplinary role)
Tissue sampling
Vascular access
Nutritional support

TABLE 51-2. TYPES OF PALLIATIVE SURGICAL PROCEDURES

In this chapter we discuss the role of palliative surgery in the management of gastrointestinal malignancies that are most commonly encountered by general surgeons and surgical oncologists. Surgical procedures are emphasized whose primary aim is treatment of symptoms and complications.

GASTROINTESTINAL TUMORS

An estimated 250,600 new cases of gastrointestinal (GI) cancers will be diagnosed in the United States in 2002 (1). Taken together, gastric, pancreatic, and colorectal cancers account for 79% of the total. The majority of these patients will not be cured and will ultimately die of their disease. Colorectal cancer is the second leading cause of cancer death in the United States, with an estimated 56,600 deaths annually. Pancreatic cancer is the fifth leading cause of cancer death, with an estimated 29,700 deaths annually, whereas gastric cancer accounts for an estimated 12,400 deaths.

Symptoms and Complications

The usual presenting symptoms and complications requiring palliative surgical intervention for patients with gastric, pancreatic, and colorectal cancer are detailed in Table 51-3. Pain is a particularly distressing symptom for patients with GI malignancies and generally is indicative of local and perineural invasion. Lillemoe noted that 37 of 137 patients with unresectable pancreatic carcinoma reported significant pain (5c). Hudis reported similar data, with 37 of 77 pancreatic cancer patients having moderate to severe pain at the time of initial referral (5d). The majority were considered to have pain secondary to extensive local disease. Locally advanced rectal cancer also commonly presents with pain because of invasion of the pelvic floor, sacral plexus, or nerve roots. Moran and colleagues reported significant pain at presentation in 37 of 125 patients who underwent palliative resections for rectal cancer (5e). Longo and coworkers reported significant rectal or pelvic pain in 12 of 103 patients with advanced rectal cancer (5f).

Pain
Gastrointestinal obstruction
Biliary obstruction
Hemorrhage
Perforation
Malignant ascites

TABLE 51-3. INDICATIONS FOR PALLIATIVE INTERVENTION

Patients with advanced-stage GI malignancies can present with bowel obstruction. Meijer and coworkers at Free University Hospital in Amsterdam reported on a consecutive series of 204 patients with gastric carcinoma (6). Twenty-six patients underwent a palliative resection, and obstruction was the primary presentation in 14 of these patients. An additional 25 patients were unresectable and underwent a palliative bypass gastrojejunostomy.

Obstruction can also be seen as the primary presentation of advanced-stage colorectal cancer. Garcia-Valdecasas and colleagues reported on a series of 53 patients with colorectal cancer who presented with obstruction over a 4-year period (7). Tumor staging was significantly more advanced in these patients compared to 135 patients with colorectal cancer who underwent elective operation over the same time period (34% Dukes stage D versus 17%). Similarly, Gandrup and colleagues reported that 59 of 156 consecutive patients who were operated on for obstructing primary colorectal cancers were unresectable and required either a bypass or a diversion procedure (8).

Extensive intraperitoneal disease can also lead to GI obstruction requiring surgical intervention. Turnbull reviewed 356 patients who presented over a 9-year period to Memorial Sloan-Kettering Cancer Center with obstruction and who previously had undergone surgery for an intraabdominal cancer (9). He identified 89 patients who had obstructing carcinomatosis confirmed at operation and noted that the tumor originated in the colon in 59 patients and in the stomach in 19 patients.

GI hemorrhage may also be seen as a complication in patients with GI tumors. Moreno-Otero and coworkers reviewed 427 patients with gastric cancer and reported 36 who presented with acute upper GI bleeding (10). Fox et al. reported that gastric malignancy was the cause of bleeding in 35 of a consecutive series of 2260 patients (1.5%) treated for upper GI hemorrhage (11).

Bleeding is a common symptom of advanced rectal cancer. In a review of 103 patients with advanced rectal cancer, Longo and colleagues reported that bleeding was the most common presenting symptom, occurring in 45% of patients (5). Similarly, Bordos reviewed 34 patients who underwent palliative abdominoperineal resection and noted that bleeding was a presenting symptom in 74% (12).

Perforation is a less common complication of advanced GI cancers. Free perforation of gastric cancer is rare and occurs in 0.9–4.0% of cases (13). Starnes reviewed colorectal emergencies treated at Memorial Sloan-Kettering Cancer Center over a 5-year period and reported only six patients with spontaneous perforation of a carcinoma (14).

Malignant ascites is a serious complication and portends an extremely short life expectancy. It occurs at a rate of 10–15% with carcinoma of the stomach, pancreas, and large intestine (15). These patients are often very symptomatic because of GI and respiratory compromise associated with markedly increased intraabdominal pressure. Effective palliation of malignant ascites remains a difficult problem. Peritoneovenous shunts were introduced in 1974 by LeVeen and coworkers for the palliation of intractable ascites (16). Early concerns about post-shunt coagulopathy and disseminated metastases appear unfounded, and these complications are rare in clinical practice. In 1992, Gough and colleagues in a prospective but nonrandomized study reported on 47 patients who were palliated with shunts (17). The shunt controlled malignant ascites in two-thirds of patients, but there was no difference in survival or quality of life when compared to patients who were treated by repeated paracentesis without surgical intervention. However, a report by Schumaker and colleagues reported on 116 shunts in 89 patients and determined that the shunts were associated with substantial morbidity and mortality and a brief and only fair relief of symptoms (18). Specifically, shunt-related complications occurred in 49% of cases. Perioperative mortality was 43%, and the authors considered that 13% was directly related to shunt-associated complications. In addition, flow had stopped in 50% of shunts within 30 days. This controversy can only be resolved by a prospective randomized trial.

Specific Tumor Sites

Gastric Cancer

The incidence of gastric cancer, which had been on the decline for many decades, plateaued during the last two decades. Nonetheless, gastric cancer continues to be a significant public health problem. An estimated 21,600 new cases will be diagnosed in the United States in 2002, with an estimated 12,400 deaths (1). The high mortality associated with gastric cancer is related to both the advanced stage of the disease at presentation and also to a lack of effective adjuvant therapies. As a result, the majority of patients with gastric cancer require some form of palliative surgery during the course of their illness. Determination of resectability frequently requires assessment at laparotomy or laparoscopy, and approximately 85% of patients undergo surgical exploration. At laparotomy, approximately half of the patients will be resected; of these, approximately 40% are considered palliative at the outset (19).

Obstruction

Many authors suggest that, when technically feasible, gastric resection offers the best palliation of symptoms and other complications caused by the neoplasm (6,19,20). Resection relieves symptoms of obstruction, contributes significantly to improving quality of life, and may also give some survival benefit (6,21). Figure 51-1 outlines an approach to gastric outlet obstruction due to obstructing gastric cancer.

FIGURE 51-1. Treatment algorithm for gastric outlet obstruction due to an obstructing gastric cancer. 5-FU, 5-fluorouracil; dx, diagnosis; mets, metastases; RT, radiation therapy; tx, therapy.

The early Memorial Sloan-Kettering Cancer Center experience, reported by El-Domeiri and colleagues in 1972, noted that of 80 patients who underwent palliative resections, 9% experienced good palliation until their demise and 76% achieved satisfactory palliation for an average duration of 6½ months (22). Meijer and coworkers reported on 26 patients with stage IV disease who had palliative resections, including 14 total and 12 subtotal gastrectomies. Obstruction and pain were the major symptoms in 20 of the patients. Fifty percent had good palliation of symptoms, whereas a further 27% had moderate palliation (6). The Norwegian Stomach Cancer Trial reported in 1989 was a prospective but nonrandomized trial, and included 1165 patients with stomach cancer, of whom 182 were recorded as undergoing a palliative resection (21). Having stratified patients according to age, debility, and stage of disease, they identified operative treatment (resection versus nonresection) as an independent prognostic determinant of survival by multivariate analysis. In all of these studies, the reported morbidity and mortality rates for curative and palliative resections are comparable. Five-year survival rates of 6–12% may be realized in these patients (19).

For most lesions a subtotal gastrectomy without an extensive lymphadenectomy is preferable. The role of total gastrectomy in this setting is controversial. In the past, palliative total gastrectomy and esophagogastrectomy, particularly for proximally located tumors, were discouraged due to a prohibitively high perioperative mortality rate (ranging between 20% and 30%), and also because there was a suggestion that the quality of life of survivors was reduced (20). However, with improvements in surgical techniques and postoperative care, total gastrectomy has been increasingly performed for palliation. In some series total gastrectomy comprises as many as one-third of cases. In 1991, Monson et al. retrospectively reviewed the Mayo Clinic experience with 53 consecutive total gastrectomies for advanced disease (23). Operative mortality was 8%, and a median survival of 19 months and good or satisfactory quality of life was achieved in 87% of patients. Butler and coworkers in 1989 described 27 patients who underwent total gastrectomy for palliation of advanced gastric cancer, with an operative mortality of only 4%, and the median survival was an impressive 15 months (24). Twenty-five of 26 patients left the hospital tolerating a solid diet. Total gastrectomy is also the operation of choice for linctus plastica.

When advanced local disease is discovered at operation, with invasion of adjacent organs, an *en bloc* resection is indicated in good-risk patients. In the Norwegian Stomach Cancer Trial, 182 patients had palliative resection. Fifty-nine percent of these patients also underwent splenectomy; resection of the pancreatic tail, transverse colon, and liver was added in 7%, 4%, and 2%, respectively (21). In a patient care study conducted by the American College of Surgeons and reported in 1993, 13,295 patients with gastric cancer were treated surgically (25). Extragastric extension was documented in 38% of patients and required an extended resection. Organs involved included the colon (3%), omentum (14%), spleen (2%), pancreas (2%), and esophagus (17%).

In patients with gastric outlet obstruction secondary to an unresectable tumor, a bypass gastrojejunostomy may be performed. However, this procedure is not without risk. Ekbom reviewed 20 patients who underwent palliative gastrojejunostomy and reported a 25% mortality and a 20% incidence of GI complications postoperatively (26). Eighty percent of survivors obtained relief of preoperative symptoms for a mean interval of 5.9 months and no patient was alive at 1 year. Similarly, Bozzetti reported a 10% mortality rate for 80 patients who underwent palliative gastrojejunostomy; the median survival after bypass was 3.5 months (19). Delayed gastric emptying (DGE) is a significant problem in as many as 20% of these patients (27). The factors that contribute to DGE include infiltration of the gastric wall by tumor, disturbance of autonomic function, and the frequent inability to place the stoma in a dependent position on the stomach. An alternative to gastrojejunostomy is the Devine antral exclusion procedure. The stomach is transected just proximal to the tumor and a jejunal loop is anastomosed to the proximal stomach. Kwok reported on 20 patients with unresectable antral carcinomas that were locally advanced and infiltrating the head of pancreas or the porta hepatis (28). All were treated by antral exclusion. There was no hospital mortality, and 17 patients were able to tolerate a diet until their demise. Patients with gastric outlet obstruction who are not candidates for surgical intervention because of associated medical risks may be palliated by percutaneous endoscopic gastrostomy tube drainage. This can also be converted to a jejunostomy tube for the delivery of enteral nutrition. Alternatively, some patients may be suitable for endoscopic placement of a stent across the obstruction (29).

For unresectable tumors of the cardia, the management options include endoprosthesis placement, endoscopic laser ablation, radiotherapy, or surgical bypass. Endoscopic endoprosthesis placement has a reported mortality rate of 15–45% and a 10% perforation rate (30). Other complications include blockage and displacement. Series using improved stents report lower risks of complications and mortality (31). Nd:YAG laser ablation is safe and particularly suited to exophytic lesions involving the distal esophagus. The ability to swallow liquids and semisolids is restored in 60–90% of patients, but repeated treatment may be required to maintain patency (32). Radiation treatment has also been used with comparable success (33). Surgical bypass is performed by anastomosing a Roux limb of jejunum to the distal esophagus above the level of the tumor. Good palliation has been reported (34).

Hemorrhage

Acute GI hemorrhage is an uncommon presentation of gastric cancer. The diagnosis is made by early endoscopy but is frequently difficult to control endoscopically. Loftus and colleagues reported on the Mayo Clinic experience with 15 gastric cancer patients who underwent endoscopic therapy for acute major upper GI hemorrhages (35). They noted that 13 of the 15 patients continued to bleed after treatment. Moreno-Otero reported on 36 patients presenting with bleeding gastric cancers (10). The bleeding was selflimited in 44%, but persistent or massive in 56%. Early emergency surgical intervention in the latter group was associated with a 23% mortality. Cheung and Branicki in 1991 reported on 52 patients, of whom 30 underwent elective and 14 underwent emergency surgery (36). The mortality rate for emergency surgery was 42.9% compared to 13.3% for elective surgery. The authors attributed the high mortality rate for emergency surgery to delay in operative intervention. Patients with a self-limited hemorrhage should have early elective surgical intervention, whereas patients with persistent bleeding should have early emergency surgery. A palliative resection is performed when feasible.

Perforation

Free perforation of gastric carcinoma is rare. It occurs in an ulcerated tumor and is usually associated with advanced stage of disease. In older series simple closure of the perforation was performed in the great majority of cases, but was associated with a mortality rate as high as 68% (37). Recently, Gertsch et al. reported on 34 perforated gastric cancers. Eighty-eight percent of patients underwent emergency gastrectomy and 88% had stage III or IV tumors. The 30-day mortality was 16% in

the resected group and the median survival was 10 months (13). Therefore, optimal palliation is achieved by early surgical intervention and by palliative resection when feasible.

PANCREATIC CANCER

An estimated 28,000 new cases of pancreatic cancer occur each year in the United States (38). The incidence appears to be increasing, with most cases occurring in the seventh or eighth decade of life. Over 25,000 deaths per year are due to the disease, making it the fourth leading cause of cancer-related mortality, surpassed only by lung, colorectal, and breast cancers. The prognosis is bleak, with an overall 5-year survival of 2–3%. Surgical resection offers the only prospect of cure. However, symptomatology is often vague, and the majority of patients present with advanced disease, which precludes potentially curative therapy (39,40).

Despite recent advances in pancreatic imaging (41,42 and 43) and the development of nonoperative techniques for the relief of biliary obstruction, the majority of patients still require an exploratory laparotomy for accurate staging and palliation (44). The most common indication for palliative intervention in this group of patients is for biliary or gastric outlet obstruction. For those who do not require a palliative procedure, exploration does not confer any benefit, and is associated with significant morbidity and mortality affecting both the quality and duration of survival (44,45).

Biliary Obstruction

Between October 1983 and October 1995, 1528 patients were admitted to Memorial Sloan-Kettering Cancer Center with a diagnosis of invasive adenocarcinoma of the pancreas. Of these, 40% were jaundiced and 28% had undergone some form of biliary drainage procedure before presentation.

For patients with an unresectable pancreatic tumor, the ideal palliative procedure for biliary obstruction should be effective in relieving jaundice, have minimal morbidity, be associated with a short hospital stay, have a low symptomatic recurrence, and maintain quality of life. In recent years there has been a trend toward nonoperative biliary drainage by either endoscopic or transhepatic routes (44,46,47,48,49,50,51,52 and 53). Randomized trials have demonstrated a reduced hospital stay and similar early morbidity and mortality with endoscopic stent placement compared to surgical bypass (54,55). However, long-term complications appear to increase, with recurrent jaundice due to occluded or dislodged prosthesis and cholangitis occurring in between 13% and 60% of cases (46,47,50,56). In patients who are expected to live longer than a few months, these complications make endoscopic palliation less than optimal.

Before the advent of minimal access surgical procedures, open surgical drainage was the only other palliative option. Surgical drainage provides excellent relief of jaundice (45,57). Despite extensive controversy in the literature (44,45 and 46,48,57), both choledochoenteric and cholecystoenteric bypasses, if selected appropriately, have similar results with regards to reducing serum bilirubin. In a recent analysis of our experience, we were unable to demonstrate any difference between these two methods of biliary diversion (45). Both procedures were associated with considerable morbidity, with complications occurring in 18%. Others have reported similar figures (44,57). It is our clinical impression that, particularly after a complicated postoperative course, some patients never regain their preoperative performance status and commence a slow, inexorable slide in their quality of life until death.

Minimal access surgery offers a new approach to this problem (58,59,60 and 61). In theory, the reduced operative morbidity in combination with a surgical drainage procedure would be of benefit to the patient expected to live longer than a few months. Figure 51-2 details our current approach to the jaundiced patient with a peripancreatic mass.

FIGURE 51-2. Management of the patient with a peripancreatic mass who presents with jaundice. byp, bypass; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; Lap, laparoscopy; PTC, percutaneous transhepatic cholangiography.

Gastric Outlet Obstruction

The role of prophylactic gastroenteric bypass in the management of patients with unresectable pancreatic cancer is controversial (45). Only 5% of patients have signs and symptoms of gastric outlet obstruction at the time of presentation; of the remainder, 8–28% subsequently develop this complication if a gastric bypass has not been performed at the time of the initial operation (62,63 and 64). Because of this risk and subsequent need for further surgery, many authors have liberally advocated the use of gastric bypass at the time of initial exploration. Proponents of this approach contend that the mortality of the initial surgical procedure is not increased by the addition of a gastroenteric bypass (63,64 and 65).

In contrast, some authors have reported a high mortality and morbidity, including an increased rate of DGE in patients undergoing gastrojejunostomy, resulting in poor palliation and prolonged hospitalization (45,66,67,68,69 and 70). Jacobs and colleagues reported a 29% incidence of DGE in patients who underwent both gastric and biliary bypass, whereas no DGE occurred in the group undergoing biliary bypass alone (69). Welvaart noted that DGE occurred in 67% of 37 patients undergoing both biliary and gastric bypass (70). A retrospective review from this institution of 297 patients with unresectable disease demonstrated that a prophylactic gastric bypass was associated with a significantly increased morbidity without improving survival (45). Only 3 of 38 patients who did not receive a gastroenteric bypass at their initial procedure required one subsequently. In all cases, duodenal obstruction was a preterminal event.

Currently, we reserve gastric bypass for the subset of patients who are symptomatic at presentation. We believe that to determine objective criteria for the selection of patients who would benefit from a prophylactic gastric bypass, a prospective randomized trial is required. In general, we consider those patients who present with obstruction subsequent to their initial presentation, or after therapy (i.e., after resection with recurrent disease) (Fig. 51-3) as good candidates for a gastric bypass, either by the open approach or laparoscopically. The relative merits of one method versus another remain to be determined. In the group of patients in whom gastric outlet obstruction is but one manifestation of their terminal illness, supportive care measures alone are instituted. It is important to identify this group of patients so as to avoid unnecessary pain and suffering.

FIGURE 51-3. Management of colorectal obstruction. mets, metastases; tx, therapy.

Pain

Abdominal or back pain is a major symptom in a significant proportion of patients with unresectable or recurrent pancreatic cancer. Often this is poorly managed, leading to distress and resulting in a major diminution in the patient's quality of life. The primary modalities in the management of pain remain pharmacologic and percutaneous celiac axis blockade. In patients undergoing surgery, however, intraoperative chemical splanchnicectomy should be considered. Celiac plexus blockade has been demonstrated to be effective in providing pain relief from a variety of GI malignancies (71). In 1969, Copping and colleagues first reported the technique for the relief of upper abdominal pain due to pancreatic cancer (72). Recently, Lillemoe and coworkers from the Johns Hopkins Hospital reported a prospective, randomized, double-blind study that compared intraoperative chemical splanchnicectomy with 50% alcohol to saline injection (2). The group receiving the chemical block had significantly reduced pain scores. Those patients without pain at the time of surgery had a significantly delayed onset of pain. In addition, patients with preexisting pain who received the alcohol blockade had improved survival compared to the control group. This exciting study awaits confirmation. Nonetheless, patients with pain who undergo an operative procedure should be considered for a chemical splanchnicectomy.

COLORECTAL CANCER

An estimated 148,300 new cases of colorectal cancer will occur in 2002 in the United States (107,300 colonic and 41,000 rectal) (1). The overall 5-year survival is approximately 50%. This survival statistic has not changed significantly over the past 20 years. One-third of patients are known to be incurable at presentation because of the presence of extensive local-regional or distant metastatic disease. When patients present with complications of advanced disease, or when patients present with recurrence of disease, an aggressive surgical approach is warranted in properly selected patients. The type of palliative procedure performed depends on the symptomatology, tumor location, and performance status of the patient.

Obstruction

Figure 51-3 outlines our approach to malignant colorectal obstruction. Apart from the patient whose colonic obstruction is a preterminal event, the majority of patients are eligible and benefit from some form of surgical procedure.

Approximately 20% of patients with colorectal carcinoma present as emergencies, most commonly obstruction (73). Gandrup reported that 95 of 156 consecutive patients operated on for obstructing colorectal cancers had advanced disease (Dukes stage C and D) (8). Ninety-seven patients had the obstructing lesion resected, with a 30-day mortality of 5%. Fifty-nine patients had palliative nonresective operations (diversion or bypass), and in 39 patients the tumor was completely unresectable. Complication rates were lower in patients who had primary resection of the tumor.

Patients who present with locally advanced or recurrent disease that is resectable are preferably treated by palliative resection, provided that there are no medical contraindications to resection and that they do not have widespread disease or very limited life expectancy (74).

The management of the patient with obstruction secondary to widespread recurrence or carcinomatosis is a particularly challenging problem. Most patients are initially treated with a trial of tube decompression. Turnbull and colleagues reviewed the Memorial Sloan-Kettering experience of 144 patients with obstructing carcinomatosis (9). Fifty-five patients with presumed carcinomatosis were treated conservatively. The remaining 89 patients required exploration. Fifty-nine patients had a colonic primary. Enteric bypass was the most common surgical procedure performed. Forty-eight of the 59 colon cancer patients (81%) were improved after surgery, and the mean duration of functioning bowel was 115 days. Lau reported similar results with 30 patients who underwent laparotomy for advanced unresectable, recurrent colorectal cancer (75). Normal bowel function was restored in 19 patients. The types of surgery performed included colonic bypass in 14 patients, resection in four, and defunctioning colostomy in four. For patients in whom either resection, diversion, or bypass is not an option, the permanent placement of a long intramural decompressive tube passed across the abdominal wall is an option. McCarthy reviewed 12 patients treated by this procedure and reported that 6 patients left the hospital and were capable of fluid ingestion (76).

Patients with widespread disease, at high risk for operative intervention, or with life expectancy less than 4–6 weeks can often have their bowel obstruction successfully managed nonoperatively. This includes the judicious (and frequently unnecessary) use of nasogastric intubation and intravenous fluids and aggressive pharmacologic approaches, including anticholinergics, antiemetics, antisecretagogues, steroids, and opiates (77,78).

Surgical Palliation of Rectal Cancer

Palliation of advanced rectal cancer requires special consideration. Locally invasive rectal cancers can present with complications of pain, hemorrhage, and ureteral obstruction (12). Pain can be a very debilitating problem for these patients. Deland wrote in 1936 (79), “There is hardly a more miserable man alive than the one with advanced rectal cancer.” Not infrequently, with sphincter muscle invasion, these patients also suffer from incontinence. The preferred palliation, if feasible, is surgical resection.

For low-lying lesions within 5 cm of the anal verge, an abdominoperineal resection is appropriate. Bordos and colleagues reported on their experience with 34 patients who underwent palliative abdominoperineal resection (12). The postoperative mortality was 3%, which was the same as for curative resection. Local symptoms were initially relieved in all patients undergoing palliative resection. More than half of these patients survived for 1 year, at which time less than onefourth had perineal symptoms related to recurrent tumor.

For lesions further than 5 cm from the anal verge, a low anterior resection with primary anastomosis is appropriate. Several authors have confirmed that primary anastomosis is safe deep in the pelvis, even in the presence of residual disease, with a low incidence of anastomotic leakage or recurrence with obstruction. In 1987, Moran et al. reported on 57 patients who had palliative low anterior resection and observed only one colonic obstruction secondary to local recurrence and one anastomotic leak (5e). Longo and coworkers in 1988 described 33 patients who had palliative low anterior resection and reported one patient (3%) who required reoperation because of an anastomotic leak and two patients (6%) who developed colonic obstruction because of recurrent disease (5f). If there are any concerns about the safety of performing a primary anastomosis, a Hartman's pouch and end colostomy is an alternative. A multimodality approach using either preoperative or postoperative radiotherapy might also be indicated.

It is important to differentiate a subgroup of patients with locally advanced colorectal cancer and infiltration of adjacent organs who otherwise have no other evidence of regional or distant metastases. This subgroup of patients, comprising approximately 10% of patients with locally advanced cancer, are node-negative and have a biologically indolent tumor. By extended *en bloc* resection, provided that negative resection margins are obtained, these patients can be potentially cured (80).

For patients who are found to be unresectable at laparotomy, a diverting colostomy may be required. However, the palliation achieved is inferior to that of resection. Incapacitating local symptoms of pain, tenesmus, incontinence, and hemorrhage commonly develop before the patient's demise. In the series reported by Moran, there were 17 diverting colostomies and the median survival was 6.4 months (5e). There were 28 diverting colostomies in the series reported by Longo. Postoperative mortality was 3.8% and the median survival was 5 months (5f).

In high-risk patients who are deemed unfit for major palliative resection of advanced rectal cancer, transanal excision may be an option. For lesions below the peritoneal reflection, electrodesiccation through an anoscope may be performed (81). Nd:YAGq laser therapy has been reported to achieve effective palliation in debilitated patients with disseminated disease (82). Eckhauser reported on 24 patients with unresectable rectal cancer who were palliated by endoscopic laser therapy (83). Seventeen patients presented with obstruction and seven with bleeding. Successful palliation and improvement in quality of life was achieved in all patients. The median survival was 15 months.

Surgical Palliation of Local Recurrence

Local recurrence occurs in 10–40% of colorectal adenocarcinomas treated for cure, and most appear within 2 years of surgery for the primary lesion (74). These local recurrences represent initial inadequate resection and occur in the pericolic fat and mesentery (84). Untreated, prognosis is poor and death is usually rapid—either from continued local extension, with the development of bowel or urinary obstruction, sepsis, perforation or bleeding, or as part of a disseminated disease pattern (85). Palliation of intractable pain and prevention and treatment of these complications are clear-cut indications for operative intervention, and often improve quality of life for these patients. These recurrent tumors often involve contiguous structures and require extended surgical resection. Pelvic exenteration has produced significant palliation and extended survival in some selected patients. Brophy et al. in 1994 reported on 35 such patients treated by pelvic exenteration for symptom palliation. Operative mortality was 3%, and overall morbidity was 47%. Quality of life was improved in 88% and median survival was 20 months (86).

SUMMARY

The challenges to the surgeon caring for the terminally ill patient are great: understanding the disease in the context of the illness, application of his/her skills of judgment and technique under difficult circumstances, and functioning as part of a team whose goals are those of the patient and family in maintaining comfort and quality of life as best as possible. But as the challenges are great, when done well, so too are the rewards.

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PALLIATIVE ORTHOPEDIC SURGERY

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Metastatic bone disease is a common cause of destruction of the adult skeleton. Bone is the third most common site of metastatic disease after the lungs and the liver. Carcinomas of the breast, lung, prostate, thyroid, and kidney frequently metastasize to bone and constitute approximately 600,000 new cases each year (8). Due in large part to the venous flow in Batson's plexus, the areas commonly involved include the vertebra, pelvis, ribs, skull, and proximal long bones. Lung carcinomas have access directly into the pulmonary vasculature and these cancers may spread to distal portions of the skeleton such as the hands and feet. There are many significant problems that the cancer patient may face once osseous metastases have occurred. These problems include pain and the inability to walk or even sit upright. Fractures are very significant as the patient experiences intense pain and the affected limb becomes virtually useless until the fracture is fixed. Progressive lesions in the spinal column may lead to very grave sequelae such as paralysis of the limbs, intractable neurogenic or mechanical pain, and loss of bladder and bowel function. Clinicians who care for patients with metastatic bone disease must strive to control pain and maintain the independence of their patients. The surgeon, medical oncologist, and radiation oncologist are the clinicians who have the greatest impact on achieving these goals. Control of metastases to bone can markedly improve the quality of life for these patients and their families.

CLINICAL PRESENTATION AND EVALUATION

There are two main presentations of metastatic bone disease (6). The first involves patients with a known history of cancer who develop metastatic bone disease, and the second is when the metastatic bone lesions herald the presence of an unknown primary cancer. The evaluation strategy employed to elucidate an unknown primary site in the second scenario is beyond the scope of this chapter. However, the evaluation and treatment of the bone metastases is identical for both clinical scenarios.

Patients with bone metastases present with pain over 75% of the time (15). The pain may be secondary to bone destruction or structural insufficiency, or from direct neurological compression. Pain from bone destruction often begins as an intermittent pain and then progresses to a constant discomfort. The pain is usually deep seated and “achy” in nature. Most patients quantify the pain as severe to unbearable. Weight-bearing pain in the lower extremities is common, and this historical finding should be sought when interviewing patients. The weight-bearing component may be so significant that patients initially resort to self-prescription of gait aids such as crutches or a cane. Eventually, each step causes such discomfort that the patient ceases to ambulate. Weight-bearing pain is a harbinger of pathological fracture. When such symptoms are noted, radiographs should be obtained without delay to assess the structural integrity of the pelvis and long bones. Pain from nerve root compression may be very difficult to recognize. The pain may be very diffuse and may or may not follow a radicular pattern. Dysesthetic pain from nerve root compression due to spinal metastases is often burning in nature and severe. Compression of sensory nerves in the thoracic spine may give a very diffuse pattern, whereas cervical or lumbar root compression often follows characteristic radicular patterns. Motor weakness is a common finding with significant lesions. Compression of the spinal cord may result in long track signs such as spasticity, hyperreflexia, and an unsteady gait. Thoracolumbar nerve compression may result in compression of the cauda equina (the nerve roots within the thecal sac distal to the end of the spinal cord). Patients may have very subtle loss of bowel and bladder function such as overflow incontinence, constipation, and difficulty voiding or defecating.

The clinician must carefully query the patient with a history of cancer and bone pain. When suspicious, the clinician has a variety of imaging modalities to use, including plain radiographs, technetium bone scans, computerized tomography scans, and MRI scans.

Plain radiographs are the most useful of radiographical studies. Plain radiographs should be obtained in both anteroposterior and lateral projections of long bones. When evaluating potential pelvic and lumbosacral spine lesions, an anteroposterior view of the pelvis and anteroposterior and lateral views of the lumbosacral spine should be obtained. It may be very difficult to localize the site of a pelvic or lumbar spine lesion. The radiographs should be carefully inspected for sites of cortical bone destruction. The findings may be subtle, so the clinician should carefully study every cortex.

If the plain radiographs are normal or only show degenerative changes, the clinician must search further. Normal plain radiographs in a patient with a history of cancer and bone pain are not sufficient to exclude the possible presence of metastatic bone disease. Up to 30–50% of “bone stock” may be destroyed before the appearance of obvious roentgenographic findings. The technetium bone scan is an excellent modality to search for an unknown location of metastatic bone disease or to evaluate the entire skeletal system for bone metastases. The sensitivity is extremely high (well over 90%) but the specificity is low. False-negative technetium bone scans may occur in patients with multiple myeloma, very early metastatic bone disease, malignant melanoma, metastatic squamous cell carcinoma, and in very rapidly destructive lesions such as lung and renal cancer. Patients may have increased uptake at sites of degenerative disease in the spine, shoulders, and knees, or in areas of previous trauma such as the ribs or extremities. Patients should never be told that they have diffuse bone metastases based on the technetium bone scan alone. Plain radiographs of areas of increased uptake are obtained and correlated with these nuclear medicine studies. With these two modalities, one can often make the correct diagnosis and plan treatment.

MRI is an excellent modality to characterize the bone marrow in a patient with increased uptake on the technetium bone scan and no or equivocal findings on the plain radiographs. The most useful imaging sequences are the coronal T1 and inversion recovery images. Metastatic lesions typically have low signal intensity on T1 weighted images and high signal intensity on T2 weighted images. When the clinician reviews the images with the radiologist, he or she should know the age of the patient, whether the patient is a smoker, and whether the patient has had chemotherapy. With a high-quality MRI scan, one can usually make the definitive diagnosis of metastatic disease. Computerized tomography scans are less useful in establishing the diagnosis of metastatic disease, as the marrow cannot be adequately studied. However, computerized tomography scans can be very useful for surgical planning in the spine and pelvis as very accurate determinations of cortical bone destruction can be made. Due to its excellent osseous detail, this modality is often of great value in ruling out subtle fractures.

TREATMENT OF METASTATIC BONE DISEASE

There are four principles in the treatment of patients with metastatic bone disease: (a) provide analgesia, (b) prevent progression of bone destruction, (c) prevent or treat fractures, and (d) maintain independence of the patient. The first two principles are intimately linked together. The pain in metastatic bone disease is usually caused by the bone destruction. When the clinician identifies the site of involvement, then treatment should begin. External beam irradiation and opioid analgesics are very effective in halting the bone destruction and controlling pain. Patients should also be evaluated by their medical oncologist for consideration of systemic treatment. Systemic treatment with hormones, cytotoxic chemotherapy, or a bisphosphonate may halt the bone destruction. Patients with breast carcinoma and multiple myeloma may have significant reconstitution of the skeleton with a combination of chemotherapy and bisphosphonate treatment.

SURGICAL TREATMENT

Surgery plays a valuable role in patients with metastases to bone. Prophylactic stabilization as part of the treatment of long bone lesions and decompression with stabilization of the spine are among the most common procedures performed. Operative management can immediately improve pain, allow mobilization, and increase independence and quality of life. Operative management can be conveniently divided into three groups: treatments of long bone lesions, pelvic lesions, and spine lesions. The goals of treatment at each of these sites are the same—pain relief and mobilization, achieved through immediate rigid fixation for stabilization and postoperative external beam irradiation to prevent progression.

The most common sites that require fixation are the femur and humerus. Other long bones that occasionally require operative intervention include the tibia, ulna, and radius. Clinicians are often required to assess a particular long bone lesion as to the need for prophylactic fixation. When studying the radiographs, one must decide whether the bone can withstand physiological loading with an acceptable risk of fracture. When one judges that the bone is too weak to withstand normal loading, then one makes the diagnosis of “impending fracture” and begins an assessment of the patient for prophylactic fixation.

Criteria for Impending Fracture

The criteria for impending fracture are far from absolute. There are a number of useful criteria in the literature (1,4,5,7,9). Clinicians use a combination of variables to predict fracture and often individualize the recommendation for each patient. The most important variables are the amount of cortical bone destruction, the pattern of bone metastasis, the location of the lesion and the location's stress concentration with activities of daily living, and the presence or absence of weight-bearing pain. It is also important to know if the patient has previously had a course of irradiation to that bony site.

Amount of Bone Destruction

The percentage of cortical bone destruction is the most important variable considered. When the amount of bone destruction exceeds 50%, the risk of fracture is significant. The amount of involved bone is determined by estimating the amount of cortical bone destroyed on both the anteroposterior and lateral radiographs (four specific cortices are thus measured and their involvement summed). Fidler has shown that fractures are unlikely to occur (2.3%) when less than 50% of the cortex is involved and very likely (80%) to occur when greater than 75% of the cortex is destroyed (4).

Pattern of Bone Destruction

Lesions may be sclerotic (blastic), mixed lytic-sclerotic, or purely lytic. Prostate, bladder, medulloblastoma, and bronchial carcinoid are the most likely carcinomas to have purely blastic metastases to bone. Blastic lesions are the least likely to fracture and the most likely to heal after internal fixation of a fracture when one does occur. In contrast, purely lytic lesions are most often seen in metastatic disease secondary to kidney, lung, thyroid, uterine, adrenal, melanoma, and gastrointestinal cancers. Lytic lesions are the most likely to fracture and the least likely to heal. Mixed metastatic lesions, often seen in breast, ovarian, testicular, lymphoma, and cervical cancers, have an intermediate risk of fracture.

Location of Lesion

There are a number of sites that are very prone to fracture; these sites are called “high stress sites.” The subtrochanteric region, femoral diaphysis, and distal femoral dia-metaphyseal regions are particularly prone to fracture as up to eight times body weight can stress some of these regions during stair climbing. When extensive disease exists, fracture may ensue with minor trauma; the bone may even fail spontaneously. The humeral diaphysis and distal dia-metaphyseal areas are also high stress sites, especially in patients using crutches or a walker. In these patients, the humerus becomes a weight-bearing bone. The femoral neck is another anatomical region that is subjected to high stresses, but less so than the subtrochanteric region.

Weight-Bearing Pain

Weight-bearing pain is an extremely important variable. When patients experience pain with every step, structural insufficiency is likely present with normal physiological loading. If the patient has significant weight-bearing pain and bone destruction greater than 30–40% associated with purely lytic bone destruction, one should consider these variables as potentiating each other and should strongly consider prophylactic fixation. If bone pain is present in a small blastic metastasis and is painful at night and at rest, then this pain may be more consistent with pain due to local periosteal or nerve stimulation, tumor biology rather than structural insufficiency of the bone.

Prior External Beam Irradiation

Significant pain after external beam irradiation may indicate either tumor progression or structural insufficiency. If significant bone destruction is present (30–40%), internal fixation to rigidly stabilize the bone and a second course of irradiation can be considered.

There are no absolutes in predicting fracture risk and surgical candidates. The criteria that have just been presented provide consistent and helpful guidelines for decision making, but the clinician must use judgment in making recommendations. Medical comorbidities and surgical risk stratification of patients certainly influence the recommendation to proceed with surgical intervention. Life expectancy and activity level before diagnosis are important variables in determining appropriateness of surgery, as well as in choosing a specific implant design for reconstruction. Additionally, serial radiographs, when appropriate and available, provide much greater insight into the biology of the lesion than does a single picture. Radiographs should certainly be followed over time in those patients considered appropriate for nonoperative management.

Specific Treatments

Long bone lesions can be treated with either internal fixation or prosthetic devices. Internal fixation devices (intramedullary rods and plates) are most commonly used. They are the treatment of choice when rigid and durable fixation can be achieved. Prosthetic devices are chosen when rigid internal fixation cannot be achieved or the joint surfaces have been compromised.

Intramedullary Devices

Locked intramedullary rods are excellent devices to achieve rigid fixation of lesions in the femur (Fig. 52-1), humerus (Fig. 52-2), and tibia. These rods are best suited for fixation of diaphyseal and dia-metaphyseal lesions. The closer the lesion is to the metaphysis, the less rigid the fixation of the locked intramedullary nail. The femoral nail has been modified so that a large screw can be placed close to the articular surface to achieve rigid fixation in the metaphysis and epiphysis (also called the *reconstruction* or *third generation femoral* nail). As the neutral axis of the nail and the femur are almost the same, the moment arm about the implant, and therefore the transmission of torque, is small. This confers excellent long-term implant survival even in the face of full weight bearing.

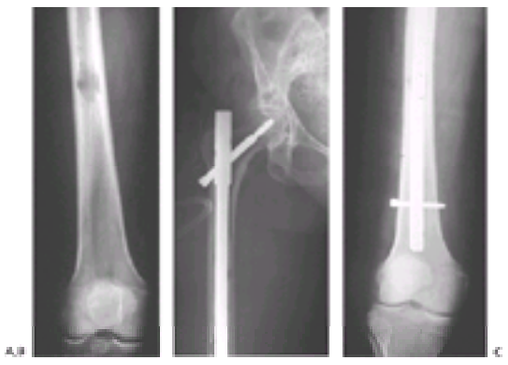

FIGURE 52-1. A: Anteroposterior right femur showing metastatic lesion with lytic destruction. **B** and **C:** After prophylactic fixation with intermedullary reconstruction nail.

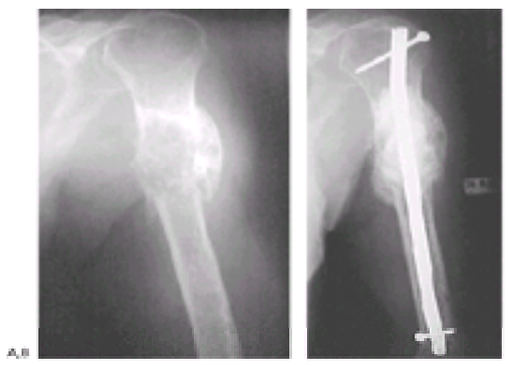

FIGURE 52-2. A: Anteroposterior left humerus showing pathological fracture of the humerus secondary to metastatic hypernephroma. **B:** After internal fixation with intermedullary nail.

Plate Devices

Plates are very useful for fixation of metaphyseal and epiphyseal lesions. There are two major prerequisites for successful plate fixation. First the joint surface must be completely intact so that the patient has a functional range of motion without pain. Second, there must be sufficient intact bone stock that rigid fixation is achieved and the patient is allowed to bear full weight after the procedure. To achieve rigid fixation such that full physiological loading is possible, at least one cortex must be almost completely intact. The plate is contoured to replace the destroyed cortex. Methyl methacrylate cement augmentation is used to supplement plate fixation in virtually all cases.

Prosthetic Devices

Prostheses are used for reconstruction of large destructive lesions and periarticular areas not amenable to internal fixation. Additionally, these devices are often used for salvage of failed internal fixation or for cases in which radiation therapy cannot be used postoperatively and therefore internal fixation would be likely to fail due to disease progression. Prosthetic devices are most commonly used in the proximal femur for femoral neck fractures and intertrochanteric lesions. Standard femoral prostheses are used for femoral neck and head lesions, whereas head and neck prosthetic devices are used for large lesions in the intertrochanteric region when there is significant bone destruction. The femoral endoprostheses are very versatile, allowing the surgeon to choose different-length stems to achieve varying levels of fixation within the femoral shaft. However, most devices are unable to extend all the way into the distal femoral metaphysis. Custom modular devices have played an important role in patients with large lesions that have been resistant to rigid fixation with standard devices, as well as when progressive disease necessitates the resection of large segments of the involved bone (11).

SPECIFIC ANATOMICAL SITES

Lower Extremity

Femur

The most commonly involved region is the proximal femur, followed by the femoral shaft and, least commonly, the distal dia-metaphyseal region. When evaluating and treating patients with femoral lesions, one should carefully image the entire femur with plain radiographs to ensure that there are not multiple areas of cortical bone destruction. If an internal fixation device ends short of an area of bone destruction, a “stress riser” is then created and the area becomes very prone to subsequent fracture at this location. Marrow replacement with no cortical bone destruction generally does not need to be bypassed by the fixation device. However, the patient must be treated with external beam irradiation postoperatively to control disease progression, which might result in cortical bone destruction.

Femoral Neck/Head

Patients with femoral neck and head metastases present with groin pain and difficulty ambulating. A careful history and examination are paramount, as these symptoms may mimic arthritis. The femoral neck is subjected to high forces during ambulating and twisting movements. Femoral neck and head lesions are treated with bipolar hemiarthroplasty after fracture or when there is an impending fracture. Smaller lesions can be effectively treated with external beam irradiation.

Subtrochanteric and Intertrochanteric Lesions

The intertrochanteric and subtrochanteric regions are common sites for femoral destruction. The reconstruction nail is an excellent fixation device for this region as the femoral neck, subtrochanteric region, and shaft can be protected with a single device. In addition the nail is easy to insert, with low morbidity (16). Only small incisions are used, and patients can bear full weight immediately after surgery. When there is a large amount of bone destruction, such that rigid internal fixation cannot be achieved, prosthetic devices are the best method of reconstruction. Head and neck endoprostheses (Fig. 52-3) can be chosen such that the intertrochanteric bone loss is replaced with the metal body of the prosthesis. Very large destructive lesions can be completely removed and reconstructed with custom modular prostheses (Fig. 52-4). The intramedullary stems of these devices are fixed with cement so that immediate full weight bearing is usually permitted.

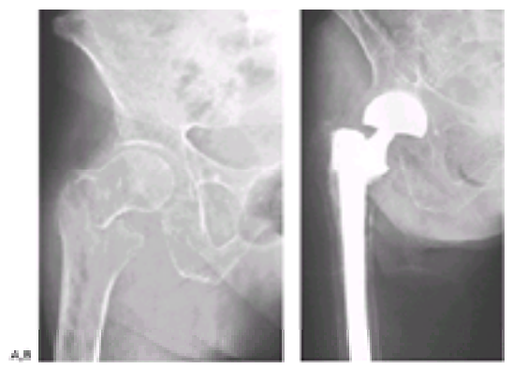

FIGURE 52-3. A: Anteroposterior right proximal femur showing pathological peritrochanteric fracture. **B:** Prosthetic replacement using a head and neck prosthesis.

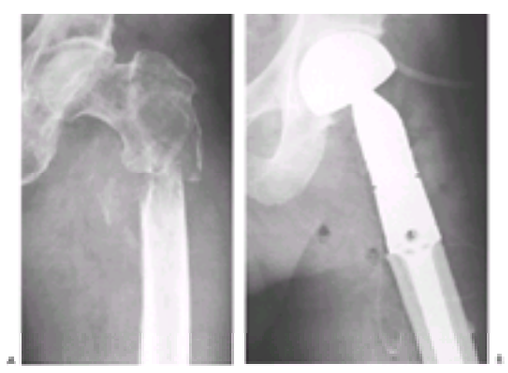

FIGURE 52-4. A: Anteroposterior left proximal femur showing metastatic lesion with extensive bone destruction. **B:** After resection and replacement with

megaprosthesis.

Femoral Shaft

Femoral shaft lesions are common and very prone to fracture. Standard interlocking intramedullary nails (Fig. 52-1) are often chosen because a wide selection of rod diameters are available. The largest appropriately sized nail should be chosen to minimize the risk of nail fatigue failure. When the bone destruction is extensive, having a large nail is very advantageous, as it may take a long time for the bone to reconstitute after external beam irradiation. Unlike standard nails, most reconstruction nails have the disadvantage of a fixed diameter through the shaft portion of the nail (e.g., 11 mm). It may not be feasible with such a design to use a larger nail, e.g., a 12-, 13-, or 14-mm nail; the larger nail is more resistant to fatigue failure.

Distal Femoral Dia-Metaphyseal Region

The distal dia-metaphyseal region can be treated with either a plate device or a retrograde nail. The closer the lesion is to the joint surface, the less rigid fixation will be with the retrograde nail. For this reason, plate fixation is often chosen over nail fixation for distal femoral lesions. Plate fixation is augmented with methyl methacrylate cement. The cement provides immediate rigidity and is very effective in structurally replacing the destroyed bone.

Tibia

The tibia is not commonly destroyed. When bone destruction does occur it is usually in the proximal metaphysis or the diaphysis. The exact same principles are applied as in the femur, with plate fixation often used for proximal lesions and rod fixation commonly used for lesions of the shaft.

Pelvis

Pelvic lesions may occur in the sacrum, ilium, periacetabular region, or the ischium. Fortunately, pelvic fractures secondary to metastatic bone disease are very uncommon. Patients become symptomatic early in the disease so that treatment can begin before significant bone destruction and fracture have occurred. Acetabular lesions pose the greatest challenge to orthopaedic surgeons and oncologists. Many acetabular lesions can be treated nonoperatively with external beam irradiation and protected weight bearing until the weakened area has healed. If fracture has occurred into the weight-bearing dome of the hip joint, then nonoperative treatment is unlikely to provide lasting pain relief with good function. If the joint is compromised or the bone destruction is so significant that healing is unlikely, then acetabular reconstruction is necessary. Acetabular reconstruction is generally done with cemented acetabular components. The surgeon must decide whether to augment the reconstruction with an acetabular ring or to cement the component in a standard fashion. Augmented reconstruction with rings should be performed whenever there is significant medial wall destruction (Fig. 52-5).

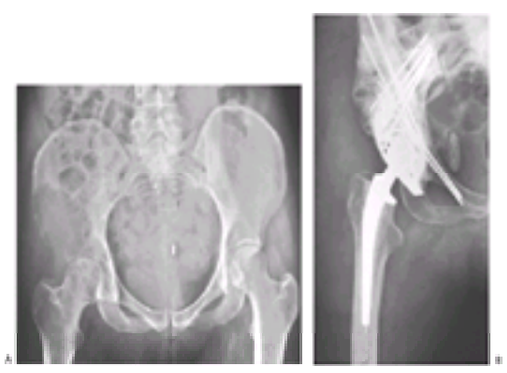

FIGURE 52-5. A: Anteroposterior pelvis showing extensive destructive lesion secondary to metastatic breast cancer. **B:** After total hip arthroplasty with acetabular reconstruction with antiprotrusio cage with Steinmann pins and methyl methacrylate augmentation used to reinforce the acetabulum.

Upper Extremity

Humeral shaft lesions are best treated with intramedullary nails. If the lesion is of moderate size, excellent fixation can be achieved by locking the nail proximally and distally without opening the fracture to augment the lesion with cement. In contrast, if the lesion is large (greater than 60– 80% cortical bone destruction), cement augmentation plays a prominent role in achieving rigid fixation. In the same manner, if a fracture has occurred and there is 50% bone destruction, cement augmentation is often necessary to achieve rigid fixation. Proximal lesions are common, and if the joint surfaces have been compromised, prosthetic arthroplasty (Fig. 52-6) is an excellent modality to achieve rigid fixation and good pain-free function.

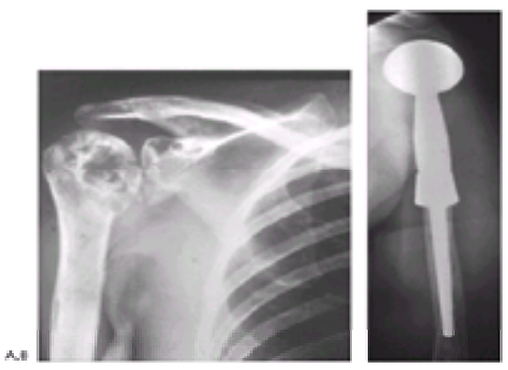

FIGURE 52-6. A: Anteroposterior right proximal humerus showing large metastatic disease involving the humeral head. **B:** After resection and reconstruction with megaprosthesis.

POSTOPERATIVE CARE

Postoperative care is an important component of the overall care of the patient. Attention to detail is important to prevent cardiopulmonary, skin, and urinary tract complications. Thrombosis is common in patients who have cancer. A specific plan to prevent thromboembolism should be carried forward in the immediate postoperative period. However, one must be cautious—especially in patients who have brain metastases, as they are prone to cerebrovascular bleeding while anticoagulated. Skin decubiti can develop quickly; prevention is the best measure. Patients should be mobilized from bed on the first postoperative day and careful attention paid to their heels (especially if they have had lower extremity surgery). Urinary tract infections are also common and should be treated to prevent seeding of the prosthetic joint or internal fixation devices. Nutritional status is of paramount importance in patients with metastatic disease. Evaluation and repletion of nutritional deficiencies, including those of protein or calorie malnutrition, must be aggressive to minimize cachexia, wound complications, immunosuppression, and anemia of chronic disease.

Hypercalcemia can be a significant problem (13). Patients should be evaluated for hypercalcemia if they develop any of the early signs, such as anorexia, fatigue, nausea, or neurological changes. The serum calcium level should be checked in the early postoperative period if the patient has a history of previous hypercalcemia; ionized calcium should be checked directly or should be calculated by the clinician.

PROGNOSIS

Unfortunately, virtually all patients with metastatic bone disease eventually succumb to the disease, with median survivals from 6 to 48 months. It is difficult to predict prognosis for the individual patient. In general, patients with breast and prostate carcinoma live for longer periods than patients with lung carcinoma. Patients with renal cell carcinoma have a variable life expectancy, with some living for long periods whereas others succumb rapidly.

Yamashita studied a group of 82 patients with metastatic breast carcinoma; the median survival was 35 months (14). In a multivariate analysis, the distribution of bone metastases and the presence of blastic metastases had a significant impact on survival. On the basis of the technetium bone scan, patients were divided into two groups, those with a cranial distribution (above the lumbosacral junction) and those with a caudal distribution (below the lumbosacral junction). Patients with a cranial distribution had a 5-year survival rate of 36% compared to 16% in the caudal group (p = .0194). Patients with blastic metastases also had a better 5-year survival compared to lytic metastases (42% vs. 23%, p = .0031). The authors noted the following favorable prognostic variables in patients with metastatic breast cancer: (a) no extraosseous metastases, (b) cranial bone metastases, (c) presence of radiographical osteosclerosis in metastatic bone lesions, and (d) no evidence of hypercalcemia. Coleman also reported additional organ involvement as a poor prognostic sign in patients with metastatic breast carcinoma to bone (3). Favorable prognostic factors included estrogen receptor positivity, a long disease-free interval (>3 years), and premenopausal status. Rana, in a study of 169 patients with metastatic prostate carcinoma, found that the number of metastatic sites had a significant effect on survival (10). Patients with either pelvis only or thoracic vertebrae only had the best prognosis (median survival 1578 and 1250 days, respectively) compared to patients with sternum and elsewhere, and skull and elsewhere who had the worst prognosis (321 and 281 days, respectively).

POSTOPERATIVE RADIATION TREATMENT

External beam irradiation is used postoperatively to arrest tumor growth and control pain. The use of external beam irradiation after surgery has been associated with a decrease in the need for second surgical procedures and improved functional status of patients with previously unirradiated long bone and acetabular lesions (12). In Townsend's retrospective study, 15% of patients treated with surgery alone required a second surgical orthopaedic procedure because of increasing pain and loss of fixation of the internal fixation device. In patients treated with postoperative irradiation, only 3% required a second procedure. If surgical intervention is deemed appropriate, then external beam irradiation should be done postoperatively to prevent delay in stabilization of an impending fracture.

External beam irradiation is generally initiated 2–4 weeks after surgery. Three thousand centiGray (cGy) in 10 fractions is commonly given to fields that encompass the original site of disease as well as the length of the prosthesis. The British Association of Surgical Oncology Guidelines from the United Kingdom recommend 2000 cGy in 5 fractions as an appropriate dose in the postoperative setting (2). Patients with renal cell carcinoma receive higher doses to control their disease (4500 cGy in 180 cGy fractions) (17).

It is critical in the treatment of these complex patients that a multidisciplinary approach among surgeons, radiation and medical oncologists, radiologists, physiatrists, therapists, and pain clinicians be used to maximize the patient's quality of life and to coordinate care in an expeditious and logical manner.

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PALLIATIVE ENDOSCOPIC AND INTERVENTIONAL RADIOLOGIC PROCEDURES

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Palliation of symptoms associated with advanced cancer can be accomplished through less invasive and more cost-efficient endoscopic and radiologic methods when compared with standard open surgical procedures. Specialization in oncologic procedures by gastroenterologists and interventional radiologists has spared many patients additional loss of time and postoperative pain associated with aggressive surgical interventions (1,2 and 3). Technological advances and refinements in endoscopic and interventional radiologic procedures have eliminated the need for extensive surgeries and possibly lengthy recuperation in these ill patients, and have decreased the risks of complications. Patency of the gastrointestinal (GI) tract affected by cancerous tumor growth or strictures caused by radiotherapy can be restored with minimal discomfort and without significant threat to the patient's well-being. Internal and external drainage systems can be placed to relieve organ obstruction pain and inanition, and to prevent life-threatening end-organ dysfunction. Table 53-1outlines palliative endoscopic and interventional procedures.

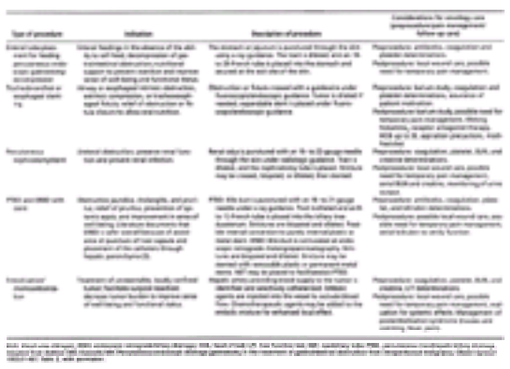

TABLE 53-1. COMMON ENDOSCOPIC AND INTERVENTIONAL PROCEDURES FOR ONCOLOGY PATIENTS

GASTROINTESTINAL TUBES FOR DECOMPRESSION AND NUTRITION

Nearly half of all patients undergoing gastrostomy and jejunostomy have cancer. Although the majority require GI tubes for enteral nutrition, gastrostomies and jejunostomies are inserted in a select group of patients for the purposes of decompression and drainage of intestinal obstructions. Approximately 40% of patients with ovarian cancer and as many as 28% of patients with colorectal cancer are at risk for developing bowel obstruction (4). Isolated malignant foci or widespread carcinomatosis of the abdomen causing external compression of GI structures are common causes of obstruction. Occlusion of the gastric outlet or intestine by tumor and adhesions from prior surgery, radiotherapy, and intraperitoneal chemotherapy are other mechanisms for gastric and intestinal blockages. Cramping and intestinal distention may be transiently relieved by vomiting, belching, flatus, and defecation; however, the unremitting cycle of these symptoms is often physically and emotionally intolerable. When initial management with aggressive pharmacotherapy, bowel rest, and temporary nasogastric decompression fails, GI decompression should be considered. Intolerable pain, fecal vomitus, intractable nausea or emesis, and esophageal ulceration are clear indications for venting gastrostomies or jejunostomies (5,6and7).

Gastrostomy and jejunostomy, whether intended for venting purposes or for feeding, can be accomplished through surgical, radiologic, or endoscopic techniques. In a meta-analysis of the efficacy and safety of each technique (8), the 30-day mortality rate (8%) was the same for both radiologic and percutaneous endoscopic approaches. Statistical analyses revealed significantly fewer complications (p <.001) and decreased mortality (p <.001) with radiologic techniques compared to surgery and percutaneous endoscopic gastrostomy (PEG). These data must be interpreted cautiously, as subset analyses were not performed.

Techniques for Gastrostomy and Jejunostomy Placement

Endoscopic Placement

Both percutaneous radiologic and endoscopic placement of gastrostomy tubes (G-tubes) and jejunostomy tubes (J-tubes) for decompression and feeding provide an acceptable alternative to the uncomfortable presence of nasogastric tubes, and eliminate the need for operative procedures. (6,9). Insertion of PEG involves a standard upper endoscopy with conscious sedation. After endoscopic examination of the stomach and duodenum to exclude significant ulcerations, the anterior gastric body or antrum is transilluminated and the gastric body is fully insufflated. Using the endoscopic light source, a suitable area on the anterior abdominal wall is transilluminated and the suitability of the site for a percutaneous tract is confirmed by gentle external compression at the potential entry site. These maneuvers allow for the determination of a safe site with the absence of any intervening viscera or major blood vessels. With some exceptions, dependent on the type of G- tube to be inserted and operator preference, a needle or trocar is passed into the gastric lumen and a guidewire is then threaded through the hollow needle and retrieved endoscopically (Fig. 53-1). The guidewire is then pulled up to the patient's oropharynx and the G-tube is passed over the wire into the stomach and out of the anterior abdominal wall. Firm traction is applied to ensure passage of the internal bolster through the esophagus and to allow a traction seal and apposition of the gastric and abdominal walls to minimize leakage of gastric contents or feedings.

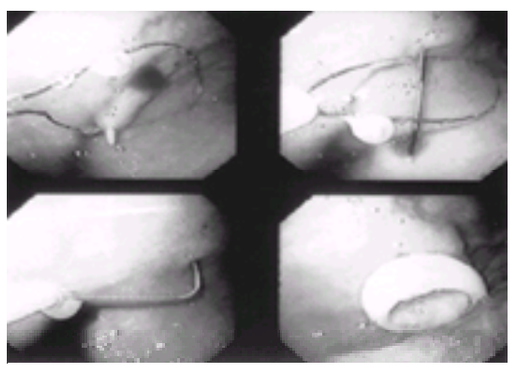

FIGURE 53-1. Endoscopic placement of gastrostomy tube. Initial introduction of trocar into gastric lumen (upper left). Guidewire passed through trocar and grasped by endoscopy snare (upper right). Guidewire fed into stomach and withdrawn to allow per os introduction of feeding tube (lower left).Appearance of gastrostomy after placement (lower right).

Recently, endoscopic ultrasound (US) has been used as an adjunct to aid in the placement of endoscopically placed G-tubes when the transillumination and indentation are not optimal (10). The advantage of this technique is that it may be performed in formerly complicated situations, including previously operated abdomens and in postpartial gastrectomy patients. The use of endoscopic US imaging significantly improves visualization of the bowel and gastric viscera, which might otherwise be impeded by the formation of adhesions, presence of taut peritoneum or ascites, or diffuse intraabdominal metastases. As a result, risks for inadvertent perforation of bowel, other organs, and metastatic foci are minimized. Studies show promising results over conventional procedures in facilitating ease of insertion and decreasing morbidity associated with the procedure (5).

Radiologic Placement

Radiologic gastrostomy is performed using fluoroscopic guidance under local anesthetic, with conscious sedation if needed. If swallowing function is intact and there is no GI obstruction, the patient is given oral contrast the night before to opacify the transverse colon and splenic flexure the next day. A nasogastric tube is placed and the stomach insufflated with air. US is used to mark the left lobe of the liver if it crosses over the stomach. The anterior wall of the stomach is then punctured through the abdominal wall under fluoroscopy, avoiding both the colon and the liver. Aspiration of air and injection of contrast confirm that the needle tip is within the stomach. One or more “T-anchors” are placed for gastropexy, then the puncture tract is dilated over a guidewire and the tube placed. In patients with aspiration risk, the pylorus is crossed and a gastrojejunostomy catheter is placed with the tip beyond the ligament of Treitz. Single- or doublelumen catheters are available, with the second lumen allowing decompression of the stomach as well as jejunal feeding. The catheter is left to external drainage for 24 hours, and the patient is monitored for peritoneal signs. If the tube is to be used for feeding, an enteral cap is placed and feeds begun with water or dextrose solution at 30 cc per hour, which is advanced as tolerated. Peritoneal leakage, procedure-induced ileus, or bowel dysmotility may limit advancement of feeds.

Complications

Technical difficulties encountered during insertion tend to be relatively low, ranging from 4% to 8% (5,7,9,11,12). The inability to implant G-tubes has been attributed to tumor invasion of anterior gastric wall, anatomical anomalies, and massive ascites (9,13,14). Overall, such difficulties seem to be noted more frequently with PEG placement than for radiologic guidance (8). Complication rates for both procedures vary from study to study, and must be cautiously interpreted in view of different methods of placement, operator experience, and diversity of patients. Procedure-related deaths, typically defined as mortality within 30 days of the procedure, have been reported (8). However, mortality rates within 30 days of the procedure may reflect consequences of the underlying disease and the overall poor status of the patients rather than direct causation from the procedure. Significant risks for complications include urinary tract infection, previous aspiration, and age >75 years (15).

Intestinal (colonic) perforation, peritonitis, and gastric hemorrhage are among the most serious complications. Isolated occurrences of mechanical intraabdominal seeding of tumor (16) and stomal seeding (17) have been reported. Although the diameter of the lumen might be expected to increase adverse effects, Cannizzaro et al. found no appreciable differences in symptomatic relief and placement-related complications between patients who received 15- and 20- French lumen catheters (5). Prophylactic use of preprocedure and postprocedure antibiotic administration has been used to reduce the incidence of infection. The data are not clear, but it appears that the preprocedure use of antibiotics reduces the postprocedure incidence of tube site cellulitis and fasciitis. Meticulous cleansing of the tube site with an iodine prep or antibacterial soap and application of a sterile gauze dressing minimizes early wound infections. Once the sutures are removed (if used) and the subcutaneous tract has sealed (in approximately 3 weeks), no additional care to the site is generally required.

Jejunostomy Tube Placement

Radiologic and endoscopic placement of jejunostomies are valuable techniques associated with low risks while avoiding the need for surgery. Tubes can be placed into the jejunum indirectly via a gastric puncture site, such as a double-lumen gastrojejunostomy tube or a J-tube threaded through a G-tube (14,18). Alternatively, direct endoscopic jejunostomy is placed using methods similar to PEG placement with good success rates, low complication rates, and high patient satisfaction (19). The tubes are inserted distal to the ligament of Treitz under conscious sedation. The advantage of this technique is the relative stability of the direct J-tube placement in comparison with a J-tube threaded through a G-tube. Insertion of percutaneous jejunostomy catheters are more easily accomplished when a J-tube has previously been present because the small bowel is adherent to the abdominal wall, creating a secure tract. The bowel loop can be punctured under fluoroscopic or endoscopic guidance, the tract dilated, and a new tube placed. The absence of a wellestablished access site makes the initial percutaneous procedure technically more difficult because of bowel mobility. In these circumstances, a gastrojejunostomy catheter may be needed. Magnetic technology, which allows for transient fixation of otherwise mobile bowel segments against the anterior abdominal wall, may allow for easier endoscopic placement of J-tubes. This has been studied in a swine model, and holds promise for direct endoscopic enteral tube placement using minimally invasive techniques (20).

Considerations with Gastrointestinal Tube Placement

Several factors must be taken into account to select the best method and site of GI tube insertion. Both radiologic and endoscopic methods have similar procedural success rates, 30-day mortality rates, and types of complications (8,14). Local expertise and patient factors should be considered in selecting the appropriate method of placement. For instance, in patients with severe pharyngeal or esophageal strictures that prevent the passage of an endoscope, radiologic guidance may be preferred (14). In other patients, who need visual investigation of the upper GI tract, endoscopic guidance is favored.

Other factors are considered in selecting the appropriate site of GI tube placement (gastric versus jejunal). Feeding gastrostomies are preferred over jejunostomies for patients who may require skilled nursing placement, as J-tubes tend to fall out and clog more frequently. Venting gastrostomies are indicated for patients with high upper intestinal or gastric outlet obstructions, whereas venting jejunostomies are more effective for decompression of intestinal obstructions that are more distal. Patients at risk for aspiration via emesis, as opposed to oropharyngeal dysphagia, are better candidates for jejunostomy feeding tubes. Through the use of a dual-lumen gastrojejunostomy tube, an artificial GI bypass can be constructed with a venting gastrostomy above the obstruction, enabling enteral feedings via a jejunostomy below the obstruction (21).

Lumen size appears to be more of an issue for patients who require intermittent or continuous decompression and wish to ingest soft food and fluids. Modifications in the contour of the tube and outflow portion, rather than lumen size, seem to be most critical in maximizing the flow of GI secretions mixed with semisolid foods and liquids (11). It is necessary to ensure that the tube selected for any patient is appropriate for its intended purpose. Some tubes now have one-way valves, which decrease the likelihood of patients expelling gastric contents if the end seal is loose, but these tubes are not suitable for gastric decompression. Most tubes are now designed in such a manner that they may be removed via firm traction and do not require repeat surgery or endoscopic procedure. Replacement button devices and stomal tubes are available.

Above all, patient and family acceptance, motivation, and ability to care for the tube or administer feedings are critically important in the successful management of GI intubation. Patients and families are instructed to (a) care for the tube exit site, (b) observe the site for any peristomal redness, ulceration, or drainage, and (c) flush, cap, and connect the tube to the appropriate devices. The tube can be anchored to the abdomen with special securing devices (Fig. 53-2). Arrangements for home health care are coordinated if patients are immediately discharged to home after tube placement, require nutritional support (enteral or total parenteral) or fluid replacement, or need additional teaching after hospitalization. This is necessary to assure proper monitoring as feeds are initiated and advanced, as well as to assist the patient and family with wound care and help them select an appropriate drainage container and operate suction devices for venting tubes.

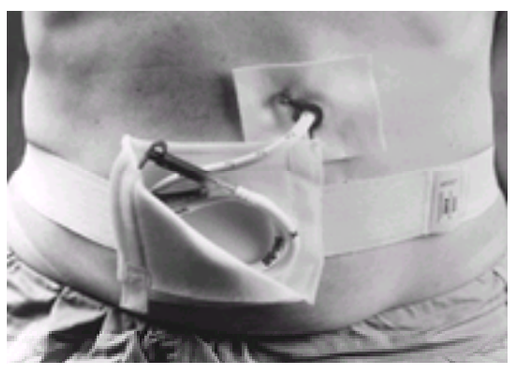

FIGURE 53-2. The Dale gastrostomy tube holder (Dale Medical Products, Inc., Plainville, MA) allows patients requiring enteral feeding greater mobility and security, and the ability to enjoy a more active, comfortable lifestyle. The tube holder secures percutaneous endoscopic gastrostomy tubes and other abdominal feeding tubes without the discomfort and irritation caused by tape and other adhesive-backed holders.

Costs associated with the procedure must also be considered. Endoscopically and radiologically placed tubes can avoid the use of the operating room and general anesthesia, and their attendant costs and risks. Charges for PEG placement have been assessed around $2400 and radiologic placement at $4500 (8). Estimated reimbursement for professional fees remains similar, and for inpatients, the hospital reimbursement for the procedure is generally embedded into the fixed rate established for the diagnostic category.

PALLIATIVE MANAGEMENT OF GASTROINTESTINAL AND BILIARY OBSTRUCTION

Malignant intrinsic obstructions or extrinsic compressions of GI structures can be relieved through the placement of endoprostheses made from materials that restore both patency and function of the esophagus, colon, rectum, and biliary and pancreatic ducts. Over the past decade a dramatic improvement in the materials, design, and delivery systems has served to make these procedures both widely disseminated and less dangerous.

Esophageal Stenting

Indications

Esophageal endoprosthetic intubation is used to treat esophageal compression from locally advanced esophageal, mediastinal, or tracheobronchial malignancies, as well as strictures that may have resulted from prior radiotherapy. Endoprostheses (stents) also allow for the palliation and occlusion of tracheoesophageal (TE) fistula, permitting oral intake. The insertion of an artificial tube restores patency of the esophagus and can provide relief from dysphagia, pain, and the inability to swallow or effectively clear oral secretions.

Relative contraindications for the placement of esophageal stents include extensive circumferential tumor growth that occludes the lumen and interferes with passage of a guidewire and dilators, necrotic lesions that may hemorrhage, friable tissues that increase the chance for perforation, anticipated discomfort associated with the presence of the stent, and lack of patient acceptance or compliance with dietary modifications and follow-up care. The stents may leave a patient with a persistent globus sensation if placed within 2 cm of the upper esophageal sphincter. The placement of a stent into a fibrotic (posttherapy) stricture or one resistant to dilatation may result in mediastinal pain, as the pressure exerted by the stent in its attempt to deploy continues until full expansion.

Types of Stents

A variety of rigid and metal self-expandable stents are available as endoprosthetic devices. Selection of stents is dependent on several factors, including life expectancy, pattern of tumor growth (e.g., location, orientation of tumor invasion, extent of invasion, size), anticipated complications, and desired treatment outcomes (Table 53-2). Rigid stents have been manufactured from several materials, including polyvinyl tubing, silicone with metal reinforcements (Wilson-Cook, Wilson-Cook, Inc., Winston-Salem, NC), radiopaque silicone with metal reinforcements (Atkinson tube, Key-Med, Inc., Essex, UK). Promising results have been reported using cuffed rigid stents in managing life-threatening sequelae associated with TE fistulas (22,23). Patients with TE fistulas tend to be poor surgical candidates because of respiratory distress, malnutrition, and debilitation from advanced stages of cancer. Mortality rates as high as 36% have been documented with attempts to surgically repair this type of fistula; however, peroral intubation using a cuffed rigid stent to seal off the fistula has reduced mortality to 24% (22). Expandable cuffs attached to rigid endoprostheses have been successful in occluding fistulas with less patient discomfort and reduced hospitalization compared to surgery, and without the risk of pressure necrosis (23).

Situation	Rigid stents	Expandable metal stents
Cancer within 2 cm of upper esophageal sphincter	--	--
Airway compression by tube	--	+
Limited life expectancy	--	--
Lack of patient motivation	--	--
Luminal obstruction preventing passage of a guidewire	--	--
Noncircumferential tumors preventing anchoring of the stent	--	+
Soft or necrotic lesions with poor anchoring qualities	--	+
Profusely bleeding lesions	-	-
Horizontal orientation of the malignant lumen	+	+
Acutely angulated, complex lesions	+	+

+, preferred; -, suboptimal; --, to be avoided if possible.

TABLE 53-2. RELATIVE INDICATIONS FOR RIGID AND EXPANDABLE METAL ENDOPROSTHESES

The introduction of metal self-expanding esophageal stents, patterned after biliary and vascular stents, has minimized problems associated with the rigid polymeric stents and their fixed lumen diameters (Fig. 53-3). Although selfexpanding metal stents are approximately ten times more expensive, their advantages of larger lumen size, ease of insertion, decreased complication rates, and greater success with more stenotic lesions often outweigh any cost expenditures. All of the metal stents share an ability to be placed into a narrow lumen on a small-bore delivery device and then allowed to expand once in correct anatomical position. Technical success rates for deployment are reported to be greater than 95%, with significant improvement in dysphagia and tolerability of oral intake (24,25,26 and 27). A variety of self-expanding metallic stents are available that differ in design, elasticity, and resistance to angulation (28). Some metallic self-expanding stents are covered with a polymeric sheet to inhibit tumor ingrowth and to facilitate occlusion of TE fistula tracts (27). Others are designed with an artificial sleeve to ideally help decrease reflux symptoms after placement for tumors near the gastroesophageal junction. Knowledge of their physical properties and tumor characteristics/anatomy can help in selecting the appropriate stent for a particular patient. Unlike rigid stents that can be taken out, metal self-expanding tubes are virtually impossible to remove short of an open surgical procedure, due to the expandable nature of the device.

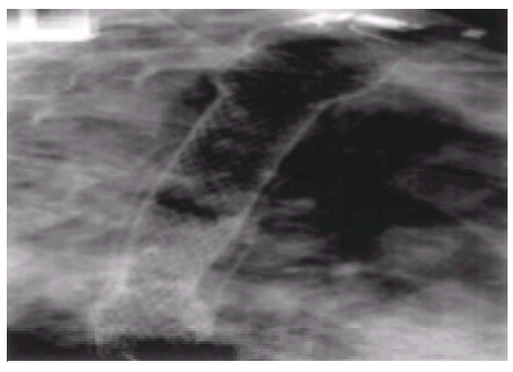

FIGURE 53-3. Fluoroscopic view of Schneider-covered esophageal prosthesis (Boston Scientific, Natick, MA) at the time of deployment.

Complications

Perforation, stent migration, pain, and hemorrhage are among the most common complications of esophageal stents. Perforation is the most serious complication and

occurs with a frequency of approximately 6–8% with the rigid endoprostheses (29,30). The rate of perforation is <3% with the metallic self-expandable stents (24,26,27,31). Perforation may occur as a result of the endoscopy, esophageal dilatation, or the endoprosthetic placement. Factors associated with a higher incidence of perforation include prior radiotherapy and surgical intervention, sharp angulation from tortuous tumor involvement, and preexisting kyphoscoliosis. In the majority of cases, perforations are identified at the time of stent placement by careful endoscopic inspection of the esophagus and pharynx, the physical examination findings of subcutaneous emphysema or crepitation of air, and radiographic detection of extraluminal air in the chest and neck areas. The exact location of a leak can be detected by the use of water-soluble contrast media.

Perforation always carries a risk for accompanying mediastinitis. Once identified, the use of acid-suppressive agents and i.v. antibiotics are the mainstays of therapy; the stent itself may seal off the site of the perforation. Consideration for the placement of an additional endoprosthetic or surgical repair needs to be entertained for open communicating tracts.

Stent migration and dislodgement may complicate metallic stent placement in up to 5% of patients (27). Some stents are designed to decrease migration (26), but further studies ascertaining their effectiveness for this complication are needed. Barium studies postprocedure document location and function of the stent, and provide a baseline should migration be suspected in the future. Tumor ingrowth occludes stents in approximately 10–60% of cases, depending on the type of endoprosthesis used, and occurs a mean of 7 weeks postprocedure (24,27).

Bleeding related to expandable metallic stent placement occurs in <5% of cases (25,27). This is often insignificant, but more serious hemorrhage requiring transfusions has been reported (25). Aspiration may occur either during the placement of the endoprosthetic or subsequently, due to reflux of gastric contents. It is important to instruct patients that they should not lie supine or prone after placement; this is especially important when the endoprosthetic bridges the gastroesophageal junction.

A persistent globus sensation may occur if the stent is placed in the proximal esophagus, within 2 cm of the upper esophageal sphincter. Mediastinal pain may occur in 5–15% of patients (24,27,31).

It is useful to have a preprocedure barium study to assess for sharp angulations, unsuspected perforations, distance from the upper esophageal sphincter, and presence of fistulas. Despite concerns over complications of esophageal endoprosthetic placement, this procedure is relatively safe and offers considerable benefits for optimizing oral nutrition and improving quality of life. Patients are advised to gradually increase the consistency of their food but to avoid solid meats, breads, and baked products.

Colorectal Endoprostheses or Stenting

Indications

The introduction of colorectal stents, designed similarly to esophageal prostheses, has successfully relieved colorectal stenosis from obstructing tumors. In some cases, endoprosthetic devices have been implanted for acute management of intestinal obstruction to allow for luminal decompression before palliative and definitive surgical resection (33,34). In other cases, colorectal stenting has been advocated as a primary palliative treatment (35). De Gregorio et al. reported survival after colorectal stents ranging from 4 to 22 months (35), and others have determined that the time to reobstruction varies from 45 to 91 days (36).

Types of Rectal Stents

Endoprostheses used to restore and maintain colorectal patency are similar to the metal self-expanding tubes inserted to alleviate esophageal compression. They are placed under endoscopic or fluoroscopic guidance. The Wallstent (Boston Scientific, Natick, MA) is a popular stent, with models constructed with diameters of 18–22 mm and deployed lengths of 60–90 mm. Plastic stents have been used; however, one study comparing this technology to metal self-expanding stents found a higher incidence of placement failure due to iatrogenic perforation and temporary incontinence with plastic material (37).

Complications

Mild rectal bleeding may occur with colorectal stent procedures. More serious complications such as perforation seem to be more prevalent among patients with local tumor necrosis. Stent placement failures tend to be related to technical malfunctions or the inability to intubate the obstructed area due to extensive tumor involvement and luminal compromise.

In a manner analogous to the placement of the esophageal endoprostheses, we have found it beneficial to obtain a preprocedure barium study, if possible, to rule out acute angulation. After colorectal stent placement, patients are advised to report signs and symptoms of increased pain, rectal bleeding, inability to defecate, abdominal distention, or stent protrusion through the anal opening. Consistent use of laxatives and stool softeners as well as dietary modifications aids in maintaining bowel regularity.

Enteral Endoprostheses or Stenting

Malignant gastric-outlet, duodenal, and small bowel obstructions may be caused by occlusion of the lumen by intrinsic tumor mass or extrinsic compression. Until recently, surgical procedures were the only palliative option for these patients. Enteral stents can replace the need for palliative surgery by providing patients relief from symptoms and allowing maintenance of oral intake (38,39 and 40).

The types of endoprostheses are similar to the colorectal stents. One of the more popular models (Wallstent-Enteral, Boston Scientific, Natick, MA) is available in lengths of 60 and 90 mm, and in diameters of 18, 20, and 22 mm. They are usually placed under endoscopic and fluoroscopic guidance. Contrast studies and abdominal computed tomography (CT) scans are helpful in defining anatomy and guiding appropriate placement. Types and rates of complications appear similar to those of esophageal and colorectal stenting, and include perforation and hemorrhage; large datasets are not yet published.

Biliary Stenting and Drainage Procedures

Indications

Palliative management of biliary obstruction or stenosis in patients with unresectable hepatic metastases, cholangiocarcinoma, and pancreatic carcinomas may improve quality of life (41,42,43 and 44). A measurable effect on psychosocial outcomes with placement of biliary stents has been observed (43).

Therapy of malignant biliary obstruction can be approached in a variety of ways. Surgical resection offers the possibility for cure, but is only possible in 10–15% of cases. Palliation can be achieved by surgical bypass or by endoscopic or percutaneous stenting combined with adjuvant radiation and chemotherapy. Comparative trials have shown no advantage between surgical versus nonsurgical palliation of the obstruction in survival (43a). Some surgeons prefer that all patients undergo preoperative biliary drainage, although a clear benefit from preoperative drainage has not been proven.

Methods of Placement

Endoscopic therapy requires retrograde cannulation of the common bile duct, performance of a sphincterotomy, and placement of a 7- to 11-French plastic endoprosthesis. A successful diagnostic endoscopic retrograde cholangiopancreatography is accomplished in 75–90% of patients, after which the technical success rate for performing a sphincterotomy is very high. For low strictures, such as pancreatic carcinoma, stent placement after successful cannulation of the duct is achieved in 95%, with a morbidity of 10% and a mortality of approximately 3% (45). Success rates for hilar strictures decline significantly to the 40–60% range, with an increase in morbidity and mortality to 18% and 8%, respectively (46,47). Higher success rates can be obtained using a rendezvous procedure, in which an interventional radiologist passes a guidewire percutaneously through the biliary tree into the duodenum, and is met by the endoscopist who pulls the guidewire out through the mouth. With this throughand-through approach, an endoprosthesis can be passed retrograde without creating a large transhepatic track. Use of the rendezvous technique increases the success rate for retrograde stenting of hilar strictures to almost 90% (48).

Percutaneous biliary drainage is successful 95–100% of the time but suffers from an acute, serious complication rate of 15%. Once internal drainage has been achieved, conversion to an endoprosthesis is almost always possible with little added morbidity (49). Advantages of retrograde endoscopic stenting are its lower morbidity and the ability to change a clogged endoprosthesis. However, the endoscopic approach to the bile duct has a lower technical success rate than the percutaneous approach. Endoscopically placed plastic stents are usually smaller than those placed percutaneously, but metal stents are of the same size. It is not possible to administer intracavitary radiation without percutaneous access. Percutaneous internal–external drainage can almost always be accomplished regardless of the level of obstruction; this allows for larger tubes, which can be easily changed. Access is maintained for brachytherapy or for later interventions as the disease

progresses.

Types of Stents

Technologic advancements in the perfection of metallic self-expanding implantable stents have maximized the efficiency of stents, but stent malfunction as a result of tumor ingrowth and overgrowth is a significant problem. Percutaneous or endoscopic deployment of metal stents has been associated with less pain during placement than plastic stents (47). The main advantage of metal stents appears to be a slightly longer duration of patency, 9–12 months.

Complications

Chronic internal–external drainage is associated with complications in up to 50% of patients, including cholangitis, skin infection, bleeding, leakage of bile and ascites, rib erosion, osteomyelitis, catheter fracture or dislodgement, and seeding of tumor cells along the track. The tubes require regular flushing and dressing. Even with optimal care, routine tube changes are necessary at 8- to 12-week intervals to avoid occlusion. For some, the distortion of their body image is psychologically distressing. Insertion of an endoprosthesis avoids many of the complications of having a chronic percutaneous catheter, but repeat drainage is required if the stent becomes obstructed.

Long-term patency rates are difficult to measure because of the high mortality in this population, but are in the range of 68–94% at a follow-up of 4–5 months (47,50,51,52 and 53). Occlusion of plastic stents occurs due to a sequence of bacterial adherence, glycoprotein deposition, and encrustation with bile salts. Newer series, employing longer stents made from smooth-surfaced polymers or antibacterial coatings, show patencies at the higher end of this range, with median patencies of approximately 6.5 months (51,54).Long-term complications are common, with cholangitis in 20% and an average occlusion rate of 11%. Stents fracture or dislodge in 3–6% of cases. Average survival with malignant biliary obstruction is only 3–5 months. In the subset of patients with more indolent cholangiocarcinomas, stent placement can significantly increase survival.

Several studies have evaluated the efficacy of metal selfexpanding stents in the treatment of neoplastic-related biliary obstruction by percutaneous insertion. Nicholson et al., who placed metal self-expanding stents percutaneously in 77 patients with inoperable biliary obstruction with no evidence of metastatic spread, found serum bilirubin levels returned to normal within 7 days of stent placement in 98.7% of patients (42). Use of metal stents may prove advantageous in patients with cholangiocarcinoma when intraductal radiation is administered via an iridium wire before stent placement, which can deliver 2000–3000 rads within a 1-cm radius. This can be supplemented by external beam therapy and chemotherapy with 5-fluorouracil. This combined modality approach can yield a mean survival of close to 2 years, with mean stent patency of 19.5 months (55). Intraductal brachytherapy does not appear to improve patency in patients with biliary obstruction from other types of tumors. In another series, successful placement and catheter longevity were noted for patients with cholangiocarcinoma (N = 31; mean survival 14 months), yet 77% of patients with sclerosing cholangitis from intraarterial chemotherapy (N = 11) experienced catheter occlusions (41).

After catheter or stent placement, patients are followed with an anticipated reduction in serum bilirubin levels and resolution of pruritus over the first 7–10 days. Signs and symptoms of pain, fever, jaundice, or leakage at the tube site at any time may be a signal of stent occlusion or dislocation. Local care to the catheter exit site with a sterile dressing is done every day for the first few days, then every 3–4 days. Patients and family members are given instructions for catheter care and when to notify the physician or nurse regarding unusual findings. The site and dressing are continually observed for signs of bile leakage. The catheter is initially placed to straight drainage, with the output measured daily. Temperature is taken at least once a day for approximately 1 week after insertion. Internal–external catheters can be capped after 24 hours to move the internal flow of bile into the duodenum. Biliary tubes require flushing thrice weekly whether capped or to external drainage. Patients with longterm external drainage systems are periodically monitored for electrolyte and bicarbonate depletion. Electrolyte loss can be avoided by reingestion of the bile.

TUMOR ABLATION TECHNIQUES

Endoscopic Ablative Palliation

Palliation of symptoms of GI malignancies may be achieved through the use of tumor ablative techniques (3). These methods may be applied endoscopically and include thermal debulking techniques (bipolar cautery, monopolar cautery, laser), tissue destruction (alcohol, chemotherapeutic agents, photodynamic therapy), and radiotherapy (after loading techniques, seed implantation). The use of any of these methods is dependent on the local expertise and resources available, as well as a multidisciplinary approach to the overall care of the patient.

Esophagus

The maintenance of esophageal luminal patency is a goal for the palliation of nutritional support and the prevention of the aspiration of saliva, as well as for allowing the patient to obtain oral gratification. Many different techniques have been used. The most commonly applied in the past was bipolar cautery, but this has fallen out of favor due to concerns over full-thickness injury, stricture formation, the need for a circumferential tumor, and technical difficulties. This technique uses a rigid bipolar probe that is inserted into the tumor; serial applications of current are made as the probe is withdrawn under radiographic or direct visual guidance.

Nd:YAG laser treatment has been the mainstay of the obliterative techniques used recently by gastroenterologists. The technique is relatively fast and inexpensive if the cost of the laser power source is spread over several specialties. Numerous difficulties, including perforation, may be encountered in its application, although careful patient selection may ameliorate these risks (56). Direct ethanol injection into tumor masses has been used with success to debulk lesions, improve dysphagia, salvage endoprostheses when overgrowth has occurred, and maintain luminal patency. Scant data are available on which to base recommendations regarding its efficacy and safety. Use of chemotherapeutic agents for intratumoral injection is in clinical trials.

Another technique is photodynamic therapy, a modality that is currently approved by the U.S. Food and Drug Administration for the palliation and restoration of luminal patency in esophageal cancer (57). Photodynamic therapy involves a two-stage process in which a photosensitizing agent is intravenously administered 1–3 days before endoscopic illumination. Several studies have shown significant improvement in dysphagia in patients with inoperable, obstructing esophageal cancer (58,59 and 60). Complications with this procedure may include perforation, stricture formation, esophagitis, and skin photosensitivity (59). Further bench and clinical research will likely lead to better hematoporphyrin derivatives, better techniques, and additional applications. Local radiotherapy (brachytherapy) may be directed and aided by endoscopic techniques, including endoscopic US. Brachytherapy markers and delivery tubes may be placed endoscopically and location of the tumor precisely determined to allow for the accurate delivery of intraluminal and external beam therapy.

Rectum

The mainstay of endoscopic debulking of colorectal neoplasms has been the use of thermal ablation techniques. Large sessile or pedunculated lesions may be effectively debulked to allow for the passage of stool or for the preparation of the colon for a resection or stent placement. These techniques are relatively easily applied in the rectum below the peritoneal reflection, without much concern for the complication of free peritoneal perforation. The use of monopolar cautery snare resection coupled with saline injection is a technique that can be readily mastered and does not require a large investment in capital expenditures. Lesions that are commonly found in the rectum (and higher in the colon) tend to be circumferential and are not easily managed by application of cautery. The majority of lesions require the use of endoscopic laser therapy, most commonly performed with Nd:YAG. The KTP laser (532 nm) is just coming into clinical use, and we have found it to be quite effective. The laser energy may be applied via a free fiber and allowed to vaporize tissue to open the lumen, or it may be used with contact-type probes to allow for precise delivery of energy and, theoretically, more controlled depth of penetration. There is a paucity of data comparing this technique with others, although data that are published support its safety and efficacy when used by those experienced with the equipment and technique.

Percutaneous Ablation of Liver Tumors

In situ destruction of liver tumors has been performed with a variety of chemical and thermal techniques. Chemical ablation is most often performed with ethanol. Acetic acid has also been used. Thermal techniques include cryosurgery, hot saline injection, radiofrequency (RF), microwave, laser, and high-intensity focused US.

Patient Selection

The best candidates for percutaneous tumor ablation are those with small tumors, and with cancers that are confined to the liver but are nonetheless unresectable due to the distribution of disease, severity of underlying cirrhosis, or other comorbid diseases. Tumors must be accessible under imaging guidance. Patients with three or fewer lesions that are no more than 3 cm in diameter are excellent candidates for percutaneous treatment. Ablating lesions between 3–5 cm is more difficult, and above 5 cm the local failure rate increases dramatically.

Chemical Ablation

Chemical ablation with ethanol causes cell death due to cellular dehydration and protein denaturation. These processes, combined with small vessel thrombosis, lead to coagulative necrosis of tissue. Intravenous access is required for sedation and analgesia. Prophylactic antibiotics are not necessary. After localization of the tumor under CT guidance or US, the skin is prepped and draped and local anesthesia administered from the skin through the liver capsule. The lesion is then punctured with a 20–22 G diamond-tip, multi-side-hole needle (e.g., Bernadino needle, Wilson-Cook, Inc., Winston-Salem, NC), passing the needle to the back wall of the tumor. Absolute alcohol is injected slowly while rotating the needle, preferably during real-time US monitoring. Alcohol is brilliantly echogenic on US, jet-black on CT. The needle is gradually withdrawn toward the proximal edge of the tumor. Injection is stopped and the needle repositioned if alcohol is observed to flow into a blood vessel, bile duct, or into the liver outside of the tumor. After completing the injection, the needle is left in place for 1–2 minutes to allow the alcohol to diffuse, then the needle is aspirated firmly during withdrawal to minimize leakage. Additional passes may be required to treat the entire tumor volume.

Lesions up to 3 cm are easily treated in a single session.Because the toxic dose of ethanol is 0.8–1.0 cc/kg, lesions 4 cm or larger usually require multiple treatment sessions. Patients can be brought back at weekly intervals for this simple outpatient procedure until the entire tumor has been treated. Pain and nausea are common during the procedure, and can be managed with medication. Patients will become intoxicated if sufficient alcohol is injected, particularly Asians with alcohol dehydrogenase deficiency. Fever and transient liver function test elevation typically occur in the days after the procedure, and do not require specific therapy. Patients can be discharged after a few hours of observation. Complications occur in 1–14% of procedures. Vasovagal episodes can occur; intraperitoneal bleeding and pleural effusion are each reported after 0.5% of procedures. Rarer complications include pneumothorax, ascites, cholangitis, abscess, hepatic infarct, biliary stricture, and tumor seeding.

Successful chemical ablation causes an area of necrosis in the liver that is larger than the index lesion. Hence the apparent size of the lesion increases on follow-up imaging. It is essential to obtain “functional” imaging that is sensitive to cellular viability. At a minimum, CT or magnetic resonance imaging scans should be obtained using dynamic scanning during the arterial phase of contrast enhancement. Positron emission tomography and spectroscopy are more sophisticated techniques for assessing tumor viability. Serum tumor markers should be followed, if elevated at baseline. Fine-needle aspiration biopsy can be performed to evaluate regions suspicious for residual or recurrent tumor.

Over 1000 cases of hepatoma treated with percutaneous ethanol injection (PEI) have been reported (61,62 and 63). Among resected specimens, complete necrosis was observed in 67–80%. Local recurrence at the treated site occurred in up to 15%. Unfortunately, regional failure is high, with 64–98% of patients developing new liver tumors within 5 years. Survival rates at 5 years are reported to be 30–50%. Although these figures are remarkably high compared to most series reporting other therapies for hepatoma, it must be remembered that PEI patients are a highly selected group with very small tumor burden.

PEI does not work as well for metastatic lesions. Because metastases tend to be less vascular and are harder than the surrounding liver, the liquid alcohol tends to follow the path of least resistance back along the needle and on to infiltrate the liver, rather than diffusing through the tumor nodule. Complete necrosis is achieved in less than half of lesions, usually in tumors <2 cm in size.

PEI has been used extensively for treatment of focal hepatomas in patients with hepatic cirrhosis. However, it is being replaced by thermal ablation in many institutions. Livraghi and colleagues reported their comparative experience with the two techniques (64). These were not prospective or randomized trials. Among 84 patients/121 lesions treated with PEI and 96 patients/106 lesions treated with RF ablation, it took over four sessions of PEI on average to ablate the entire tumor, versus only 1.2 sessions for RF. Complete success as judged by imaging studies was similar for both modalities, but the local recurrence rate was 13% after PEI versus 2% for RF. There was one complication in the PEI group, five in the RF group. The conclusion was that RF is more efficient and effective than ethanol in ablating hepatomas.

Acetic Acid

Acetic acid was first proposed as an ablation agent by Ohnishi and colleagues, who reasoned that acetic acid, used in vitro to dissolve lipids and extract collagen from various tissues (including cirrhotic liver), may have applications in percutaneous ablation (65). Ohnishi initially demonstrated acetic acid to be superior to ethanol in cell kill in a rat model with a higher degree of necrosis and more homogenous diffusion. The cytotoxic mechanisms of acetic acid are similar to those of ethanol, including protein denaturation and dissolution of basement membrane and interstitial collagen resulting in coagulative necrosis of tumor cells. Dose– response studies in a rat model have shown the cytotoxic effects of acetic acid plateau at a concentration of 50% (approximately 8 mol/l). Acetic acid has an advantage of infiltrating the septae and capsule of tumors, whereas ethanol does not cross tumor septae. As a result, a smaller volume is required to achieve the same degree of cell kill with fewer treatment sessions.

These characteristics may account for the differences observed by Ohnishi and coworkers in the only prospective, randomized trial comparing ethanol ablation with acetic acid ablation for small (<3 cm) hepatocellular carcinomas (66). A total of 31 patients underwent acetic acid ablation and 29 patients underwent ethanol ablation of one to four discrete tumors. The groups were well matched in terms of age, sex, underlying liver disease, Child-Pugh score, and tumor burden (size, number, and histological grade). All patients underwent acetic acid or ethanol ablation by the same operator, using US guidance and a 22-G needle. The number of treatment sessions and total volume injected for all sessions was less with patients treated with acetic acid compared to those treated with ethanol. A significant and substantial difference was observed in cancer-free and overall survival. The 1- and 2-year cancer-free survival rates were 83% and 63% in the acetic acid group and 59% and 33% in the ethanol group. The 1- and 2-year overall survival rates were 100% and 92% in the acetic acid group and 83% and 63% in the ethanol group. No major complications occurred in either group; the minor postablation effects of pain and fever were seen in both groups.

Large-volume injections of acetic acid (greater than 20 cc) should be avoided because of the potential for metabolic acidosis and direct renal toxicity of acetic acid. Preliminary observations indicate that acetic acid may be especially useful when treating hepatic metastases, which are notoriously difficult to treat with ethanol due to their hard, firm consistency. Acetic acid appears to infiltrate through firm lesions more homogenously than ethanol.Acetic acid may also hold promise in the treatment of nonhepatic neoplasms.

Thermal Ablation

Temperatures above 60°C cause cell death within minutes. This can be accomplished with various energy sources, including RF, microwave, laser, or high-intensity US. Of these, only RF electrocautery is commercially available in the United States. Heating has advantages over chemical ablation, in that it does not depend on direct contact with the cells. Energy is dispersed fairly evenly across the treatment volume, and is not limited by septations or areas of necrosis or fibrosis within the tumor. RF ablation works by inducing ionic agitation in the surrounding tissues. This results in localized frictional heating. Lesion size is proportional to the power of energy delivered (Watts), time, and size of the probe. Reliable thermal lesions up to 3.5 cm can be created using a radial or multiprobe array.

The ablation technique is similar to PEI. IV access is essential, as pain is a significant side effect of the procedure, and deep sedation or anesthesia may be required. Access to the lesion is obtained under imaging guidance, using local anesthesia. If necessary, multiple overlapping burns are performed to treat the entire tumor volume. Each burn takes 10–30 minutes, so the procedure is more time-consuming than PEI.

Immediate results of RF ablation based on follow-up imaging indicate absence of any enhancing tumor in 60–90% of tumors, with lesion size being the major determinant of success (67,68). Local recurrence rates have been reported to be from as low as 2% to as high as 40% within 1 year. As with any local approach, new lesions are the predominant mode of failure, occurring in up to 65% of patients within 1 year. Complications occur in approximately 2.4% of cases.

Combined Regional and Local Therapy

Chemoembolization (see section Chemoembolization), although treating a large volume, is limited in its ability to induce complete tumor necrosis. Conversely, RF ablation causes thorough tissue necrosis within a small volume, primarily limited by blood flow. Hence, combining the two techniques is an appealing approach to intermediate size lesions. Occlusion of the hepatic artery or portal vein during RF ablation results in substantially larger burn volumes. This is routinely done during intraoperative ablation, using the Pringle maneuver to temporarily reduce hepatic blood flow. Temporary balloon occlusion, embolization, or chemoembolization to devascularize the tumor allows effective RF ablation of tumors up to 8 cm in diameter. Blood flow to the surrounding liver is still preserved via the portal vein, so a “surgical” margin is not achieved. Experience with this combined modality therapy is still preliminary, so long-term follow-up for recurrence is not available.

Chemoembolization

Malignancies in the liver present one of the most challenging problems in clinical oncology. Other tumors that are less common but frequently develop fatal hepatic metastases despite a resectable primary include ocular melanoma, neuroendocrine tumors, and the rare GI sarcomas. Response rates of hepatoma and metastatic colorectal cancer to a variety of systemic chemotherapeutic agents are no better than 20–40%, and a significant survival benefit has not been demonstrated. Intraarterial chemotherapy using continuous infusion of 5-fluorodeoxyuridine and steroids delivered by percutaneous catheters or by surgically implanted pumps has

remained a popular regional approach to hepatic malignancies and colorectal metastases to the liver, although none of the phase III trials comparing intraarterial to i.v. chemotherapy for metastatic colorectal cancer has shown a long-term survival benefit for intraarterial infusions (69,70,71 and 72). Response rates of hepatoma to intraarterial chemotherapy are 50–60%, with an increase in survival to 20–60% at 1 year (73,74).

Embolization of the hepatic artery has proven effective for palliation of liver metastases from carcinoid and islet cell tumors, with response rates of 80–90% (75,76). Hepatoma has a more modest response to embolization (50–60%), with some increase in short-term survival (77,78). The efficacy of embolization is limited by the liver's ability to develop collateral blood supply when the hepatic artery is occluded. For this reason, benefits from hepatic artery embolization tend to be transient. Embolization has not been shown to extend survival for patients with colorectal metastases (79,80). Chemoembolization combines hepatic artery embolization with simultaneous infusion of a concentrated dose of chemotherapeutic drugs. Theoretical advantages of this technique include the following: (a) embolization renders the tumor ischemic, depriving it of nutrients and oxygen and decreasing drug resistance; (b) tumor drug concentrations are orders of magnitude higher than those achieved by infusion alone (81,82); (c) blood flow is arrested, prolonging the dwelling time of the chemotherapy with measurable drug levels present as long as a month later (83,84); and (d) most of the drug is retained in the liver, minimizing systemic toxicity. A variety of chemotherapeutic drugs and embolic agents are used around the world. Doxorubicin, in doses of 40–80 mg, is proably the most commonly used single agent. Often it is combined with cisplatinum (100–150 mg) or mitomycin-C (10–20 mg).These drugs can be dissolved in their powdered form directly in radiographic contrast. This solution can be injected directly, or emulsified with iodized oil (Ethiodol, Savage Laboratories, Melville, NY) before injection. Embolization is completed with small particles of gelatin sponge or polyvinyl alcohol sponge.

Critical to the selection of patients for regional therapy is tumor confinement to the liver. Patients with minimal or indolent extrahepatic disease may be candidates if the liver disease is considered to be the dominant source of morbidity and mortality. Tumors that typically meet these criteria include hepatoma, intrahepatic cholangiocarcinoma, and metastases from colorectal cancer, ocular melanoma, neuroendocrine tumors, and sarcomas. When the parenchyma is diseased, the liver becomes more dependent on the hepatic artery for its blood supply. Subgroups of patients have been identified who are at high risk of acute hepatic failure after hepatic artery embolization. They typically have >50% of the liver volume replaced by tumor, lactate dehydrogenase >425 IU/l, aspartate aminotransferase (AST) >100 IU/l, and total bilirubin >2 mg/dl (85). The presence of hepatic encephalopathy or jaundice is an absolute contraindication to embolization. Biliary obstruction is also a contraindication. Even with a normal serum bilirubin, the presence of dilated intrahepatic bile ducts places the patient at high risk for biliary necrosis in the obstructed segment(s) of the liver.

Evaluation for chemoembolization includes a tissue diagnosis, cross-sectional imaging of the liver, exclusion of extrahepatic disease, and laboratory studies. Given the significant discomforts, hazards, and expense of this treatment, its palliative role should be clearly understood. After hydration and premedication with antibiotics and antiemetics, diagnostic visceral arteriography is performed to determine the arterial supply to the liver and confirm patency of the portal vein. The origins of vessels supplying the gut, particularly the right gastric and supraduodenal arteries, are carefully noted to avoid embolization of the stomach or small bowel. Once the arterial anatomy is clearly understood, a catheter is advanced superselectively into the right or left hepatic artery, depending on which lobe holds the most tumor, and chemoembolization is performed. The patient receives intraarterial lidocaine and i.v. fentanyl or morphine sulfate to alleviate pain during the embolization. After the procedure, vigorous hydration, i.v. antibiotics, and antiemetic therapy are continued. Opioids, prochlorperazine, and acetaminophen are liberally supplied for control of pain, nausea, and fever. The patient is discharged as soon as oral intake is adequate and parenteral narcotics are not required for pain control. Approximately one-half of patients are discharged in 1 day, and most of the rest within 2 days. Oral antibiotics are continued for another 5 days, and antiemetics and opioids are continued as needed. Follow-up includes return for a second procedure directed at the other lobe of the liver 3–4 weeks later. Depending on the arterial anatomy, two to four procedures are required to treat the entire liver, after which response is assessed by repeat imaging studies and tumor markers. Eighty to ninety percent of patients suffer a postembolization syndrome, characterized by pain, fever, and nausea and vomiting. The severity of these symptoms varies tremendously from patient to patient, and they can last from a few hours to several days. Serious complications occur in up to 5%of procedures.

Major complications of hepatic embolization include hepatic insufficiency or infarction, hepatic abscess, biliary necrosis, and nontarget embolization to the gut. With careful patient selection and scrupulous technique, the incidence of these serious events collectively is 3–4%. Other complications include renal insufficiency and anemia requiring transfusion, with incidences of <1% each. Thirty day mortality ranges from 1% to 4%.

Among combined series of 800 patients with unresectable hepatocellular carcinoma treated with chemoembolization in Asia, Europe, and the United States, response rates as measured by decreased tumor volume and decreased serum a-fetoprotein levels were 60–83% (83,86,87). Cumulative probability of survival ranged from 54% to 88% at 1 year, 33% to 64% at 2 years, and 18% to 51% at 3 years. Survival varies inversely with tumor volume, stage, and Childs class. Despite the large volume of single-institution experiences with chemoembolization of hepatoma published over the past decade, few controlled trials have been reported. A multicenter European trial comparing cisplatin/Lipiodol gelfoam chemoembolization to no therapy in 100 patients with relatively small tumor burdens (90% stage I) found 1-year survivals of 62% and 43%, respectively, and 2-year survivals of 38% and 26% (88). A French multicenter trial of 127 patients with more advanced disease (62% stage II or III) showed almost identical survival rates in the chemoembolization arm (64% and 38% at 1 and 2 years), with survival in the control arm of only 18% and 6%, respectively (p<.0001) (89). Several reports of chemoembolization for liver metastases from colon cancer have been reported (90,91). These consistently show a response in two-thirds of patients, and median survivals on the order of 2 years, which is approximately double that seen with systemic chemotherapy alone. A phase III randomized trial is now under way to evaluate the benefit of chemoembolization in addition to standard chemotherapy in this disease.

REGIONAL ANALGESIA

Interventional radiologists, to a limited extent, perform regional anesthetic techniques such as intercostal and pleural analgesia that can provide superior temporary analgesia during many thoracic and upper abdominal procedures. Intercostal access to the liver and kidney can be extremely painful due to irritation of the pleura and adjacent rib periosteum, especially if a temporary drain remains in place after the procedure. Interpleural analgesia and pleural blocks are especially helpful in controlling pain during procedures that involve the chest wall (i.e., pleural biopsy, thoracentesis, pleural sclerosing) (92), liver and biliary tree (i.e., liver biopsy, percutaneous biliary drainage, and stenting), and kidneys (i.e., renal biopsy, percutaneous nephrostomy), as well as providing long-term relief of intractable pain in the thorax and upper abdomen. Temporary pleural blocks may also be considered for patients undergoing radiologic placement of drainage catheters for difficult-to-localize empyemas, and more permanent neurolytic blocks for thoracic and lumbosacral pain (93). Interpleural analgesia has demonstrated safety and efficacy in the treatment of both postoperative and diffuse thoracic cancer pain (94,95).

Celiac plexus blocks (CPBs) with local anesthetics have been used to temporarily control pain associated with percutaneous biliary drainage, which is performed to gain access to the intrahepatic and extrahepatic tree for the purpose of biopsy, biliary endoscopy, and stent placement (96). This technique has significant advantages in relieving severe visceral pain that arises from biliary tract dilation and manipulation, which can be difficult to manage with sedating agents and opioids alone. Most studies document positive outcomes with CPB during procedures; however, investigators have recently proved that CPB was no better than midazolam hydrochloride and fentanyl in reducing pain (96). The mean elevation in heart rate in this study was significantly lower in the CPB group, favoring this form of regional analgesia to i.v. opioids for patients with cardiac disease. For more information on regional analgesic techniques, refer to Table 53-3. CPB using a neurolytic agent such as alcohol or phenol can be performed by anesthesiologists, surgeons, interventional radiologists, and gastroenterologists (guided by endoscopic US) to gain long-term control of pain from hepatic metastases and pancreatic carcinomas (Fig. 53-4).

TABLE 53-3. REGIONAL ANALGESIA

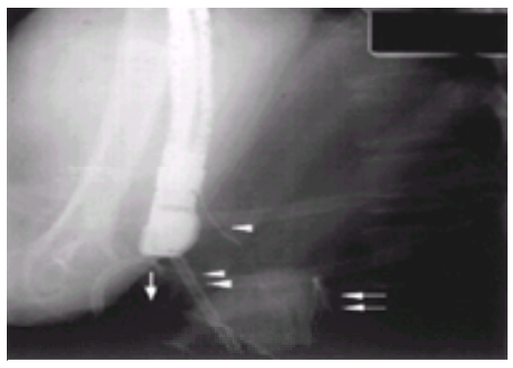

FIGURE 53-4. Radiograph demonstrating complete nonsurgical palliation from unresectable pancreatic cancer causing biliary and duodenal obstruction and with accompanying hypercoagulable state with deep venous thrombosis and visceral pain. Needle exiting Pentax endoscopic endoscope at time of celiac axis neurolysis (arrowhead). Percutaneously placed internal biliary drain (double arrowhead). Schneider-uncovered endoprosthetic in duodenum restoring patency after obstruction (percutaneously placed and endoscopically dilated to full diameter) (arrow). Percutaneously placed vena cava filter (double arrow).

CONSCIOUS SEDATION AND ANALGESIA

Interventional techniques for palliation are aimed at relieving pain and improving symptoms. However, in some circumstances these procedures may transiently worsen pain, exacerbate other symptoms, and sometimes, create new temporary sources for pain. The need for pain control before, during, and after procedures cannot be overestimated. Uncontrolled pain leads to a release of catecholamines that stimulates the sympathetic nervous system, which can stress the cardiovascular system, resulting in tachycardia, cardiac arrhythmias, or cardiac ischemia (97). It can also result in elevated blood pressure, which in turn may increase the risk of stroke and potential for hemorrhage at the procedural site (98). Nausea, vomiting, and bradycardia, which are parasympathetic responses, can accompany severe pain originating from the viscera or peritoneum as the result of an invasive procedure.

As areas of the body are manipulated, nociceptors (free nerve endings) are activated, giving rise to various painful sensations that may or may not be similar to the pain of cancer. A painful stimulus to viscera or organ structures, such as inflammation, that is sustained over time increases the vulnerability of visceral nociceptors to stimuli that would not normally evoke pain (99). The slightest manipulation of visceral structures affected by cancer pain can provoke significant pain. Moreover, ischemic pain caused by embolization procedures or damage to vasculature is so severe that adequate pain control during and after remains a clinical priority (100,101).

To some extent, the perception of pain can be diminished by percutaneous and intravascular local anesthetics, regional blocks, and liberal use of systemic opioid analgesics and sedating agents. Nonpharmacologic methods, such as relaxation techniques, can reduce the need for opioids and sedating agents, enhance amnesia, and improve the patient's overall well-being and outlook on the procedure (98). The level of complexity and duration of the procedure have warranted more liberal use of sedating agents and intensive monitoring in endoscopic and interventional radiology procedure units. Specific details are beyond the scope of this chapter and the following recommendations.for the selection of sedating agents and opioids to manage procedural pain and anxiety that accompany interventional procedures for cancer (9,102,103 and 104).

CONCLUSION

Decisions for endoscopic and interventional radiologic techniques must be based on available data and sound judgments, balancing potential risks and benefits. The ability to perform some palliative interventions is largely the result of local expertise and the availability of clinical resources. All possible comfort and supportive care measures should be considered or attempted before the undertaking of invasive interventions. Moral, ethical, and social issues arise if patients are subjected to these procedures only to prolong intense pain and suffering when life expectancy is very limited. On the other hand, withholding therapeutic options for palliation of intolerable and unmanageable symptoms takes hope away from patients for a better quality of life for the remaining weeks or months of life.

Gastroenterologists and interventional radiologists may overlap in areas of expertise and perform similar procedures; however, each offers unique aspects to the technical performance of the procedure. Careful patient selection and knowledge of the local expertise and areas of interest of each specialist leads to a multidisciplinary effort and more options and opinions in regard to the therapy for the individual patient. Differences in how each specialty approaches an individual clinical situation may be readily evident, but despite these differences, the indications for treatment and the intended outcomes for treatment remain similar.

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54

PSYCHOSOCIAL CONSEQUENCES OF ADVANCED CANCER

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Despite significant progress in research and treatments, the diagnosis of cancer creates fear and turmoil in the lives of every patient and family. In many respects cancer generates a greater sense of dread than other life-threatening illnesses with similar prognoses (1). Some studies have found that cancer patients are sicker and have more symptoms than noncancer patients in the year prior to death, and most often, it is easier to predict the course of the illness (2).

Frequently, the greatest concern of cancer patients is not death, pain, or physical symptoms, but rather the impact of the disease on their families (3). According to the World Health Organization (4), family refers to those individuals who are either relatives or other significant people as defined by the patient. Health care professionals must acknowledge the role of the family to maximize treatment outcomes. If the family is actively incorporated into patient care, the health care team gains valuable allies and resources. Families are the primary source of support and also provide the caregiving roles for persons with cancer. Of note, women comprise the majority of individuals who serve in these caregiving roles (5,6).

Although access to ongoing palliative care could potentially provide needed support for both patient and family, resources for palliative care are consistently limited. In the United States most palliative care is invested in hospice programs, but only one-third of all cancer patients receive formal hospice care, often only in the final days of life (7,8). Furthermore, a discussion concerning a referral to hospice can seem quite sudden and to the patient and family may be experienced as rejection. Despite the sobering survival statistics for many cancers, relatively few hospitals have developed a continuum of cancer care which informs patients and families that most antineoplastic therapy is palliative and not curative. This is particularly significant given that the majority of cancer patients overestimate the probability of long-term survival (9). The transition from a period of primary therapy to a period without such therapy can be very difficult and it may be surmised that the situation is worse for other chronic life-threatening diseases. At present, patients and family members enter hospice care, which is the primary deliverer of comprehensive palliative care services, and attempt to accept that prolongation of life is no longer the goal of care. In addition to the shift in the focus from cure to care, the patient and family experience the loss of the health care team with whom trust has been imbued over months and sometimes many years. The loss occurs simultaneously at multiple levels. Although palliative care at the end of life should be a time of refocusing and resolution, the referral process may cause an iatrogenic crisis rather than comfort.

PSYCHOLOGICAL RESPONSES TO ADVANCED CANCER

The psychological impact of advanced cancer and its management is directly influenced by the interactions among the degree of physical disability, internal resources of the patient, the intensity of the treatment, side effects, and other adverse reactions, and the relationship with the health care team.

Adaptation to this phase of the illness begins with an appraisal of the extent of harm, loss, threat, and challenge that this experience generates. In many respects this appraisal is linked to the intensity and quality of the patient's emotional response. Overall, this primary appraisal and definition of the meaning of advanced cancer results in an assessment of the extent of the potential harm, which then requires a secondary appraisal to occur. In this secondary level, patients must assess their personal (internal) and social (external) resources necessary to begin to address the demands and problems associated with advanced cancer (10).

In addition, two salient timelines or continua related to patient and family adaptation must be considered. The level of psychological distress forms the first continuum and the second consists of the predictable and transitional phases of the disease process. Patients with a preexisting high level of psychological distress can experience significant difficulty with any attempt to adapt to the stressors associated with a cancer diagnosis. Although most patients experience significant distress at the time of their diagnosis, the majority of patients gradually adjust during the following 6 months (11). Evidence indicates that the best predictor of positive adaptation is the psychological state of the cancer patient prior to the initiation of any therapeutic regimens (12).

Figure 54-1 details potential interventions along the disease and distress continua. The level of psychological vulnerability also falls along a continuum from low to high distress and should guide this selection of interventions. In addition, problem-solving interventions have been demonstrated to reduce distress among cancer patients as well as among family members (13,14 and 15). Prevalence studies demonstrate that one of every three newly diagnosed patients (regardless of prognosis) need psychosocial or psychiatric intervention (16,17,18 and 19). As disease advances, a positive relationship exists between the increase in the occurrence and severity of physiological symptoms and the patient's level of emotional distress and overall quality of life. For example, a study of 268 cancer patients with recurrent disease observed that patients with higher symptomatology, greater financial concerns, and a pessimistic outlook experience higher levels of psychological distress and lower levels of general wellbeing (20).

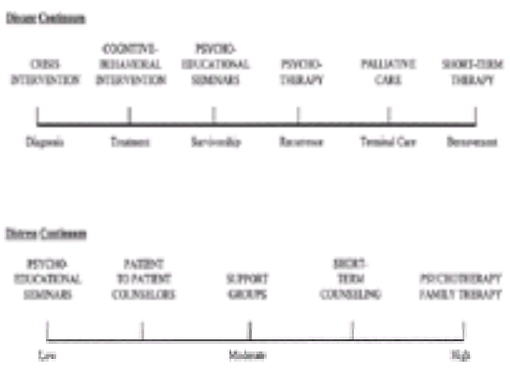


FIGURE 54-1. Continuums of care for cancer patients and their families.

If distress levels can be identified through techniques such as psychosocial screening (21), patients can then be introduced into supportive care systems earlier in the treatment or palliative care process. Accordingly, any attempt to identify vulnerable patients and families in a prospective manner is worthwhile. Screening techniques are available through the use of standardized instruments which are able to prospectively identify patients and families that may be more vulnerable to the cancer experience. Preexisting psychosocial resources are critical in any predictive or screening process. In one approach, Weisman et al. (22) delineated key psychosocial variables in the format of a structured interview accompanied by a self-report measure (Table 54-1). However, in hospitals, clinics, or community agencies which provide care to a high volume of patients and family members, a structured interview by a psychosocial provider is seldom feasible. Consequently, brief and rapid methods of screening are necessary. Brief screening techniques that examine components of distress, such as anxiety or depression, can be incorporated into the routine clinical care of the patient. Early psychosocial interventions may be less stigmatizing to the patient, and more readily accepted by patients, families, and staff if

screening identifies the management of distress as one component of comprehensive care (23). Screening is also a costeffective technique for case identification in comparison to an assessment of all new patients (24).

Social support	History	Current concerns	Other variables
Marital status	Substance abuse	Health	Education
Living arrangements	Depression	Religion	Employment
Number of family members and relatives in vicinity	Mental health	Work Finance	Physical symptoms
Church attendance	Major illness	Family	Anatomical staging
	Past regrets	Friends	
	Optimism versus pessimism	Existential	
		Self-appraisal	

From Weisman AD, Worden JW, Sobel HJ. Psychosocial screening and intervention with cancer patients: a research report. Boston: Harvard Medical School and Massachusetts Hospital, 1980, with permission.

TABLE 54-1. VARIABLES ASSOCIATED WITH PSYCHOSOCIAL ADAPTATION

Standardized measures of psychological distress can differentiate patients into low, moderate, or high degree of vulnerability. Patients with a low level of distress may benefit from a psychoeducational program which can enhance adaptive capabilities and problem-solving skills; high distress patients may possess psychosocial needs that require individual psychotherapy or family therapy along with psychotropic drug therapy for the patient. For some patients ongoing mental health services are essential, whereas other patients may require assistance only at critical transition points. Clinical practice suggests that virtually all patients could benefit from some type of psychosocial intervention at some point along the disease continuum, especially at the end of life. Psychosocial interventions include educational programs, support groups, cognitive-behavioral techniques, and psychotherapy (25). To further facilitate the process of screening, the Brief Symptom Inventory-18 was developed to create greater ease with administration and scoring and to identify gender-based norms (26,27).

The second continuum relates to the predictable phases of the disease process. This disease continuum extends from the point of diagnosis to cancer therapies and beyond. As patients move across this continuum, they may acquire experiences, knowledge, and skills that enable them to respond to the demands of their disease. The needs of a newly diagnosed patient with intractable symptoms differ significantly from a patient who has advanced disease and no further options for curative treatments.

The patient and family may be supported throughout the illness process and the family requires continuing support following the death of the patient. At times families are overwhelmed by the illness, and as a result are unable to effectively respond. For some families a death may represent a loss of the family's identity and may paralyze the family's coping and problem-solving responses. Failure to respond and problem-solve leads to a lack of control and may generate a significant potential for a chronic grief reaction (28). Although the disease continuum consists of specific points, Table 54-2 identifies a series of predictable and relevant crisis events and psychosocial challenges that occur as patients and families confront advanced disease.

TABLE 54-2. ADVANCING DISEASE AND PSYCHOSOCIAL TREATMENT

FAMILY ADAPTABILITY AND COHESION

The Circumplex Model of Family Functioning, as developed by Olson et al. (29), categorizes families in a manner that explains the variation in their behavior. Although not specifically developed for cancer, this model conceptualizes families' responses to stressful events based on two constructs, adaptability and cohesion. End-of-life care simultaneously generates significant stressors for both patients and families, especially in issues related to power, structure, and role assignments. Adaptability reflects the capability of a family to reorganize internal roles, rules, and power structure in response to a significant stressor. Given the impact of advancing cancer on the total family unit, families must frequently reassign roles, alter rules for daily living, and revise long-held methods for problem-solving. Dysfunction in the family can relate to either low adaptability (rigidity) or excessively high adaptability (chaotic). A family characterized as rigid in its adaptability persists in the use of specific coping behaviors even when they are ineffective. Those that exhibit high adaptability create a chaotic response within the power structure, roles, and rules of the family; such families lack structure in their responses and attempt different coping strategies with every new stress. Although the majority of families are in the more functional category of “structured adaptability,” 30% are rigid or chaotic. These latter families are likely to exhibit problematic behaviors such as excessive demands of staff time or interference with the delivery of medical care that the health care team may find difficult to manage (30).

The second construct of Olson and colleagues— cohesion—is indicative of the family's ability to provide adequate support. Cohesion is the level of emotional bonding that exists among family members, and is also conceptualized on a continuum from low to high. Low cohesion (disengagement) suggests little or no connectedness among family members. A commitment to care for other family members is not evident and, as a result, these families are frequently unavailable to the medical staff for support of the patient or in the decision-making process. At the other extreme, high cohesion (enmeshment) blurs the boundaries among family members. This results in the perception by health care providers that some family members seem to be just as affected by the diagnosis or treatment, or by each symptom, as the patient. Enmeshed families may demand excessive amounts of time from the health care team and be incapable of following simple medical directives. These families are not able to objectively receive and comprehend information which may be in the best interest of the patient. Also these families may assume an overprotective position in relation to the patient and may speak for the patient even when the patient's self-expression could be encouraged.

When engaging families, it is necessary to gain an appreciation for the rules and regulations of particular families. Each family has its own rules, regulations, and communication styles. In gaining an understanding of the role of the patient in the family, it is helpful to ask the patient to describe the specific responsibilities he or she performs in the family, especially during a crisis. Generalities are less informative than descriptions of the specific experiences and duties of each family member during a crisis. These queries enable the patient to openly communicate and objectively evaluate his or her role and importance in the family system and provide a clinical opportunity to assess ongoing progress or deterioration. Patients and families can usually tolerate even the worst news or the most dire prognosis as long as it is framed within a context in which the patient and family know how they are expected to respond and that the health care team will not abandon them.

IMPACT OF PHYSICAL AND PSYCHOLOGICAL SYMPTOMS

Patients with advanced illness experience pain, dyspnea, fatigue, nausea, anxiety, depression, sleeplessness, and many other symptoms that impair quality of life. These noxious symptoms also compromise cognition, concentration, and memory (31), and override the underlying mental schema of patients. For the person in pain or acute physical distress, perception is confined to only the most immediate and essential elements of his or her sensory experience, and there is only a distant remnant of a past or future. The immediate need and goal is to stop or minimize the noxious experience. In some sense, pain and other symptoms absorb the limited psychic energy of the patient, and valuable energy can only be made available if physical distress is effectively managed. The psychic life is subservient and dependent to the bodily experience.

Moderate to severe pain is reported by 30–45% of patients undergoing (32) cancer treatments and 75–90% of patients with advanced disease (33). Pain seems to

stand alone in its ability to gain the active attention of others while dramatically demonstrating a sense of being alone and vulnerable. This is especially true of patients with advanced disease, and their families. While a patient is experiencing pain, another person only inches away is incapable of truly understanding what is so central and undeniable to the patient. This invisible and almost palpable boundary between the person in pain and his or her caregivers has significant implications for the quality and effectiveness of the therapeutic relationship (34).

Given that cancer pain can be adequately managed in almost all circumstances, its deleterious and at times lifethreatening impact on the physical, psychological, and spiritual resources of both the patient and family are not only unnecessary but are evil. There is no known benefit to unrelieved pain. There are many known negative consequences. For example, Chochinov et al. (35) found that the desire for death was correlated with ratings of pain and low family support but most significantly with depression. Given the relationship between pain and depression, the importance of adequate pain management can hardly be overstated. Recently Cobb et al. (36), in their comprehensive review of the delirium literature, found that poor pain control was identified as the number one cause or contributor for delirium. Given the obvious importance and prevalence of delirium as an indicator of quality of life at the end of life, this is very important information.

Serlin et al. (37) were able to demonstrate that there is a positive correlation between pain intensity and function. As expected, low levels of pain intensity cause low levels of interference with life, while moderate to high levels of pain make it virtually impossible to have meaningful interactions with others and to feel part of a larger whole. Clinical experience consistently demonstrates that people with physical illness accompanied by high levels of pain intensity experience acute isolation and are unable to advocate for themselves and are at very high risk to be badly cared for even in the best medical centers. Family and health care providers can be sensitive, caring, supportive, and concerned, but if pain is not adequately managed, the person confronting death has little possibility to think clearly, express his or her concerns, make a contribution and to have anything resembling a peaceful death.

It is generally accepted that pain is poorly managed despite the availability of effective therapies (38,39 and 40). Patients, families, and professional staff may share a reluctance to use opioid analgesics even when life expectancy is quite limited. A primordial evolutionary process continues to exist which enables patients to accept suffering and allows the health care team to permit the unnecessary pain to occur. This type of response represents an adaptive, but “dark side” of human nature. Although most cancer patients are psychologically healthy (16,41), inadequately managed cancer pain and other symptoms can produce a variety of “pseudopsychiatric” syndromes which are anxiety-provoking and confusing to patients, families, and clinicians. Cancer patients with pain are also more likely to develop psychiatric disorders than cancer patients without significant pain (42). In the short-term, pain provokes anxiety; over the longterm, it generates depression and demoralization.

The differences between depression and demoralization as clinical constructs have yet to be empirically explored. Depression is significantly related to higher levels of cancer. pain and pain is likely to play a causal role related to depression. Overall depression rates for cancer patients are 20–25% (42) and estimates as high as 50–70% have been applied to populations with advanced disease (43). Demoralized patients are disheartened or discouraged by their circumstances but not in a pathological sense. There is a significant correlation between affective disorders and pain and among the negative emotional states associated with pain (dysphoria, hopelessness, guilt, suicidal ideation, etc.). Anecdotal clinical experience consistently demonstrates that once pain and related distressing physical symptoms are relieved, and suffering, anxiety, depression, demoralization, and suicidal ideation are ameliorated, the impact on the family is equally significant (44).

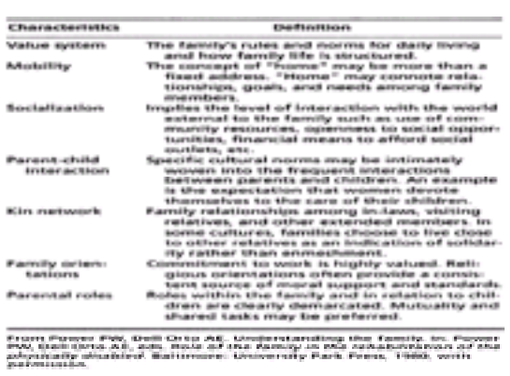
Depressed patients distort reality and grossly minimize their perceived abilities in managing the demands of the illness and its treatment. Furthermore depressed cancer patients with inadequately controlled pain are at increased risk of suicide (35,45). For the depressed patient, acute sensitivity to physical sensations may lead to or exaggerate preexisting morbid or catastrophizing thoughts. The complex and interactive associations among physical sensations (neutral or noxious sensations), mentation (personal meaning given to the sensations), and behaviors (attempts to minimize threat and regain control) are all negatively influenced by depression. The destructive synergy of unrelieved pain and depression may lead to overwhelming suffering in patients and families and to a shared sense of hopelessness and helplessness (46). Consequently a patient or family may develop the faulty perception that suicide is their only remaining vestige of control. From this perspective, the value of a multimodality approach that combines pharmacology, supportive psychotherapy, and cognitive-behavioral skills training is clear (47). From a psychological perspective promotion of compliance with medical regimens, correction of distorted cognitive perceptions, acquisition of coping skills to manage physical tension, stress and pain, and the effective use of valuable physical energy to maximize engagement of life become the focus of care.

SOCIOCULTURAL INFLUENCES ON PATIENT AND FAMILY ADAPTATION

Perceptions of illness and death can be conceptualized as experiences with both conscious and unconscious associations. These perceptions include concerns and fears that are beyond the limits of objective knowledge. Sociocultural beliefs may soothe anxiety or fear by providing comfort when a vacuum exists due to a lack of experience in the management of a chronic illness. Sociocultural attitudes also exert considerable influence as patients approach the ends of their lives (48,49). These beliefs and attitudes are evident in direct observations of how the family cares for the patient, views of an afterlife, or rituals related to how the corpse is to be managed.

Koenig and Gates-Williams (50) offer a framework to assess cultural responses relevant to palliative care. This framework, which is consistent with a comprehensive psychosocial assessment, posits that “culture is only meaningful when interpreted in the context of a patient's unique history, family constellation, and socioeconomic status. . . Dangers exist in creating negative stereotypes—in simply supplying clinicians with an atlas or map of 'cultural traits' common among particular ethnic groups.”

Patients and their families can simply not be adequately understood without knowledge of their sociocultural backgrounds (Table 54-3) (51). Patients and families vary according to interests, beliefs, values, and attitudes. Individuals learn attitudes or values through family interactions and these patterns influence how patients respond to the health care team. Although the health care team represents expertise, safety, and authority, it is also an external and foreign force, which only through necessity has gained influence and power within the family system. In stressful situations the patient and family may project their own perceptions about themselves onto the health care team.



Characteristics	Definition
Value system	The family's rules and norms for daily living and how family life is structured.
Mobility	The concept of "home" may be more than a fixed address. "Home" may connote relationships, goals, and needs among family members.
Socialization	Implies the level of interaction with the world external to the family such as use of community resources, openness to social opportunities, financial means to afford social outlets, etc.
Parent-child interaction	Specific cultural norms may be intimately woven into the frequent interactions between parents and children. An example is the expectation that women devote themselves to the care of their children.
Kin network	Family relationships among in-laws, visiting relatives, and other extended members. In some cultures, families choose to live close to other relatives as an indication of solidarity rather than enmeshment.
Family orientations	Commitment to work is highly valued. Religious orientations often provide a consistent source of moral support and standards.
Parental roles	Roles within the family and in relation to children are clearly demarcated. Mutuality and shared tasks may be preferred.

From Power PW, Dell Orto AE. Understanding the family. In: Power PW, Dell Orto AE, eds. Role of the family in the rehabilitation of the physically disabled. Baltimore: University Park Press, 1988, with permission.

TABLE 54-3. FAMILY CHARACTERISTICS SUSCEPTIBLE TO CULTURAL INFLUENCES

Although cultural characteristics are important these influences often diminish over time as families are assimilated into the predominant culture. Second-generation families are more similar to the host country than the country of origin. First-generation immigrants may possess oldworld attitudes and values about authority and illness, whereas the perspectives of their offspring will be more consistent with the health care team.

Given the many and complex demands already made on health care professionals and the rapidly increasing diversity of institutions, is it reasonable to expect that staff to be informed about the myriad of cultures represented in such a pluralistic environment? For example, it is estimated that there are over 150 different languages spoken among the native Americans, with each tribe having its own rituals around end of life (52). One can only imagine trying to provide bereavement services to a group that demands that the name of the deceased never be mentioned again? Or that even mentioning the word death will cause the event to happen? These barriers to effective and open communication, so respected by health care professionals in the United States, are not unique to native Americans (53). Furthermore, evidence exists that African-Americans are far less likely to discuss end-of-life issues due to a belief that these discussions may result in less care being delivered (54).

Although there is no formula to making a connection with another person when he or she is ill, there are some areas that can be explored together that can be mutually enriching. The health care provider needs to specifically ask the patient and family about them as a system patient, family, tribe, group, etc. Some examples are

- Since everyone is different, can you teach me how to help you get the information you need about your illness?
- How would you like me to share information with you about your illness?
- How much information, if any, would you like me to share with your family and others?
- Is there a particular person you would like me to include when you and I talk about serious matters?

- Would you like me to give you an overview of what is happening to you each time we meet or would you like me to simply answer your specific questions?
- What is your understanding of your health right now?
- What kinds of information would you like me to tell you?
- You have a very serious illness. Some people want to know what they have to prepare for in the near future. Is there anything that you would like to know?
- Is there anything you think we need to share with your family and others that may be helpful to them and you?
- Is there anything we can do together to make this time meaningful for you and your family?
- Would you feel comfortable contacting me if you have any questions?

Ultimately, a relationship is always between two people at a time. Opening up one's self to be taught by the patient and family about who they are and how they want to manage the illness is the perfect counterpoint to the awesome power held by the health care professional.

PRINCIPLES OF EFFECTIVE PATIENT AND FAMILY MANAGEMENT

The family, as defined by the patient, is virtually always the primary supportive structure for the patient. The family serves as a supportive environment, which provides instrumental assistance, psychological support, and consistent encouragement, so that the patient seeks the best available medical care. Early in the diagnostic and treatment planning phases, a family's primary functions are to instill hope and facilitate communication. For the patient whose disease is beyond life-prolonging therapy, caregiving becomes the primary focus for the family. In the latter situation, families must prepare psychologically and financially for the experience of life without the patient (anticipatory grief). Cancer and its treatments are always a crisis and an assault on the family system. As an uninvited intruder, cancer challenges the viability of the family structure to tolerate and integrate a harsh and threatening reality which cannot be overcome by force, denial, or even joint action. Joint action can be successful in terms of adaptation, and if the goals are clearly defined, there is an ongoing plan that promotes the optimal opportunity for successful goal attainment.

The health care team can guide the family in developing a problem-solving approach to the demands of the illness. The plan must be clearly communicated because it delineates each individual's responsibility so that the potential for goal-attainment is maximized. For many families with histories of effective functioning, the cancer experience represents the first time that their joint action may not overcome an external threat. Consequently, the cancer experience must be reframed into more realistic terms so that the threat can be perceived as manageable rather than destructive. If this is not achieved, the family can manifest anger, avoidance, displacement, or other forms of regressive behavior. For the family with a history of multiple defeats and failures, the cancer experience may be perceived as more evidence that they are incapable of managing the demands of an overwhelming world. The cancer experience temporarily alters the family structure, but it also has the potential to inflict permanent change. The health care team can significantly influence how these changes are interpreted and integrated into family life.

Patients often identify the effect on the family as the most upsetting repercussion of the cancer (3). Therefore, any effective intervention must include the patient, the family, and other social support networks. When patients consider their families, they may experience guilt, shame, anger, frustration, and fear of abandonment. Family members may experience anger, fear, powerlessness, survivor guilt, and confusion as they attempt to care for the patient. Family members may demonstrate the defense mechanism of displacement, transferring emotion from one person or situation to another and potentially confusing health care professionals. This confusion can create tension for family members and providers at a time when clarity and effective interactions are essential.

With little exception, assessment of the primary players in the family system is a rather straightforward process. The patient can be asked directly the following:

- Who do you rely on most to assist you in relation to the practical needs of your illness (e.g., transportation, insurance company negotiations)?
- When you get scared or confused, with whom in your family are you most able to talk?
- Who in your family most concerns you?
- Is anyone in your family overwhelmed with your ongoing medical and practical needs?
- Who in your family is coping least well with your illness?
- Is anyone in your family openly angry with you because of your illness?
- Are you particularly worried about how a specific person in your family is coping?
- Are you ever concerned that the demands of your illness will be too much for your family?
- Who is most dependent on you in your family?
- For what are they dependent on you?
- What would happen to your family if you were unable to maintain your present level of functioning?

The answers to these questions communicate to the patient and family that it is appropriate and necessary to gauge the impact of the cancer and its treatment on their lives and also provide the groundwork for the coordination of patient and family functions. In addition, role-modeling of open communication provides an environment of emotional support, flexibility in roles, and the implied and spoken promise never to abandon each other. This cannot be achieved unless the patient and family accept that some treatment effects and life events are beyond their control and there are limits to what is possible. The medical team has the responsibility to manage the physical aspects of the disease while the patient and family actively strive to integrate change, maintain normalcy, and accept the reality of the illness. The course of the illness—including death— must be identified as one of the potentially uncontrollable issues so the patient and family can focus on areas that are amenable to their influence.

Financial resources are virtually always a major concern of patients and families. When discussions of money and resources occurs within the family system, shame and guilt are common. These emotions are frequently alluded to but not openly discussed. This can be a barrier to open communication and can lead to patient fears and fantasies of abandonment. This is especially true for patients with advancing disease. Simultaneously the family may have concerns about life goals after the patient's acute need is past or death occurs. The expected range of emotional reactions within the family include anger, fear, guilt, anxiety, frustration, powerlessness, and confusion. Cancer confronts people with the reality of limitations.

In addition to the increasing costs of health insurance and home care, there are a wide variety of nonreimbursable, illness-related costs that can be financially devastating to patients and families. Transportation, nutritional supplements, temporary housing, child care, and lost work days are but a few examples of costs borne almost totally by patients and families for which there is seldom any form of reimbursement (55). Schulz et al. (56) found that respondents spent more than $200 per month on health-related expenses and reported significant negative effects on amount of time worked. Other studies have confirmed the negative financial impact of advanced cancer (57,58).

Money is almost always a metaphor for value, control, and power (59). How patients and family members communicate about money can be an indication of their perceptions of whether treatment is progressing or not. Thus interchanges about financial matters can actively represent latent communications about the perceived but unexpressed value of care and its potential outcome. For example, the patient and family may at the beginning of treatment state that money is no object and all resources must be expended so that the patient survives. By the end of treatment, however, a much more sober and realistic view concerning valuable and vanishing resources may become evident, and a greater discussion of investment and return may ensue. At this point in time, both patient and family may be actually talking about their ability to persevere. Concerns about money may then be an expression of exhaustion, diminishing hope, or anger. It is important that this metaphorical communication be seen as inadequate for open and direct communication. A metaphor is a signal and cue that indicate the need for open discussion. Openness is essential for the patient and family to discuss both their common and increasingly diverging needs. Patients and families must discuss their physical and spiritual fatigue, as well as specific financial concerns related to diminishing resources as a result of their struggle with cancer. The following clinical example illustrates a number of these points.

A 54-year-old married woman with three adolescent daughters expressed concern to the medical team about the ongoing cost of care for her terminally ill husband. The team felt that she was selfish and that it was unethical for them to consider the financial impact on the family in caring for the patient. Sensing their resistance to her plight, she felt rejected and became irate. A meeting with the patient, family, and relevant staff was organized by the social worker to openly address her financial concerns. The family had existing financial debts due to past medical treatments and consequently had ample reason for its concern related to the additional costs of care. Once this meeting resolved concerns over additional unneeded expenditures, the focus shifted to the much more emotionally laden issues related to the slow deterioration of the patient and the family's intense grief over the impending loss. It became evident that money for the family represented the loss of “everything.”

In some cases, the family may begin to perceive the dying patient as already being deceased. Anticipatory grief and premature emotional withdrawal from the dying patient creates confusion and a sense of terror in the patient. As a result, the family experiences guilt and shame because they are prepared for the loss but the patient is still alive.

SPECIFIC PROBLEMATIC PATIENT AND FAMILY BEHAVIORS

Physicians almost always identify “difficult families” as one of the most challenging tasks as a medical provider. Within the context of the family milieu, conflicts with staff may be unavoidable. It is the management of these conflicts that will determine the quality of the relationship between the patient, family, and professional staff. Conflicts may result if a family cannot follow simple guidelines or is intolerant of any physical discomfort that the patient may experience. Families that frequently criticize staff may be held to more rigid standards of behavior. Unit guidelines become laws, and the struggle for control results in fear and mistrust. Conversely,

patients and families who endear themselves to staff through verbal praise of the quality of care often receive warmth and flexibility, and, as a result, unit guidelines, such as visiting hours or number of visitors, may be relaxed.

The professional staff must be flexible in their communication styles or they may be perceived as violating family boundaries. This type of interaction can devolve into a battle for power and control. Conflicts that remain at the level of power and control make it virtually impossible to work with the patient and family to develop action-oriented, problem-solving strategies which unite all in a common set of values and goals. Effective symptom management is essential to engage the patient, family, and the staff toward a common goal. Poor management can lead to estrangement and abandonment (60). Open communication can establish goals within the context of the family and significantly reduce the strain. However health care providers must accept that at times any approach may be ineffective because the family structure cannot tolerate the influence of external forces. When this occurs continued attempts at open communication is the only alternative that can achieve some sense of mutual understanding and trust.

Families can exhibit a range of behaviors that the health care team defines as problematic and can potentially interfere with the delivery of medical care. Families can delay or prevent the completion of a procedure, verbally abuse the staff, or divide the team. Families may demand excessive amounts of staff time, repeatedly demanding sessions to review the same information. Confusion may reflect intense anxiety and the overwhelming nature of this experience for caregivers. Some families have unrealistic expectations and compare the responses of staff members searching for inconsistencies. Others fail to follow unit guidelines, consistently arriving well before visiting hours or delaying their departure from the hospital at the end of the day. Families may encourage patients to refuse medical recommendations or directives. Family members at times may speak for the patient and encourage the patient to withdraw and regress. Families may also possess unrealistic expectations of staff. Family members may perceive the staff as their own medical providers and seek personal care from the team.

Family functions include facilitation of medical decision making, reduction of stress, initiation of effective problem solving, and provision of comfort to the patient. If the family cannot provide these functions or is unavailable to the patient and staff, the staff may need to assume and fulfill these roles. At times, the staff may be resentful when families are unavailable or withdraw from participation. The burden on staff to care for these patients can be dramatically increased.

SPECIAL PATIENT AND FAMILY ISSUES

Children in the Home

Children of adult cancer patients may be an unseen and forgotten population. In acute care settings, children are not observed due to the patients' daytime appointments or policies that prohibit visits to inpatient units. Within the palliative setting, however, children and grandchildren are often present and may play an active role in the caregiving process.

Although salient developmental differences exist among children of different ages, those 3 years or older are able to verbally communicate their concerns so that an ongoing dialogue can occur. Highly sensitive to emotional and physical changes, children benefit most from an environment where they are continually given information in a manner that they can understand and are then encouraged to ask questions. Adults should be prepared for questions to be rather concrete and egocentric, centered around the immediate needs of the child and any potential change in the immediate family. Children are specifically concerned about the continued presence of parents and their own safety. Questions from children usually come one or two at a time. Children often need time to interpret and integrate the adult responses before returning for additional information, which may occur days or weeks later.

Methods to deliver medical information or relieve distress must vary according to each child's developmental stage. Children have fantasies about the etiology, meaning, and duration of a parent's illness. Young children need consistent information about the chronic nature of the disease so that they can anticipate changes and incorporate an understanding of these medical events into their world. Young children cannot fully appreciate the concept of permanence. The permanence of death or abstract terms, such as “forever,” are beyond their ability to integrate. Children need consistent support, measured doses of information, and an environment that can respond to their questions.

Developmentally, adolescence is the time for resolution of conflicts with parents as well as a quickened pace to individuation from the family. These processes can be delayed or significantly complicated by the family's focus on a loved one who is slowly deteriorating and dying. Competitiveness, sexuality, aggression, and peer relationships may compound and confuse attempts to cope with a loss and the end of a specific relationship.

Familial roles can be disrupted or confused during a parent's illness, and, as a result, adolescents may be required to assume adult responsibilities. There is a danger in treating an adolescent as an adult. The demands of adolescence under normal circumstances generate numerous stressors for the family, and a chronic illness at this point in the life cycle can significantly exacerbate the family's level of distress. Of particular concern, adolescents may be “parentified.” Physical maturity should not be equated with emotional, intellectual, or spiritual development. Adolescents can easily be overwhelmed with guilt and shame when their normal sense of power and grandiosity cannot control symptoms or death. This may have a long-term negative effect on the ability to tolerate emotional relationships. If the death of a parent or grandparent is to occur in the home, children must be carefully assessed, and appropriate interventions and support should be offered.

Psychiatric Illness

Histories of psychiatric disorders present further challenges in the effective management of patients and families. Psychiatric symptoms must be assessed and appropriately managed if the patient is to truly benefit from supportive care interventions. For example, symptoms, such as severe depression, may dramatically influence a patient's perception of pain and the ability of the health care team to control it. Furthermore, psychiatric symptoms of a family member can also cause a significant concern given the health care team's expectations concerning caregiving in the home by family members. Frequently expectations of family members as caregivers are relatively uniform despite the significant variation that exists in each family's level of functioning. Families must be assessed not only for their availability but also for their ability to provide adequate supportive care.

Patients or family members with a history of physical or sexual abuse may exhibit significant difficulty in the ability to develop a trusting relationship with the health care team and may require psychiatric management. Families with a history of abuse may try to withhold information related to the abuse and any attempt to assess the patient or family as an intrusion. Trust can only be developed over time as the health care team consistently verbalize their concern for patient and family as well as their availability for support and intervention. Families with severe dysfunction isolate and protect themselves from the outside world with rigid outer boundaries. Health care providers may define such a family as problematic when initial offers of assistance are refused. The team may experience frustration and rejection, which is inevitably communicated directly to the patient and family. Consequently, the family is lost as an ally and resource and as a result their isolation is increased. Although few in number, timely psychiatric referrals for these patients and family members are essential.

Addictions

A current or past history of substance abuse or an active addiction within the patient or the family creates a sense of alarm within the health care team. For example, the patient with a history of substance abuse may not be trusted by health care providers. The patient's behavior may be viewed as manipulative and if pain is a problem, there may be reticence to prescribe higher opioid doses if the patient is in pain, or even when dying.

Patients should not needlessly suffer as a result of a prior history of opioid abuse or their current treatment in a methadone clinic. Patients with a history of opioid addiction that is remote or has been effectively managed in a drug treatment program may be at much greater risk for the undertreatment of cancer pain. Consultation with a drug treatment facility may be necessary to plan effective management strategies.

Family members of a substance abuser can negatively influence or reinforce the patient's drug-seeking behavior.These families frequently possess a high level of cohesion, which can be characterized as enmeshed. Within this type of family, boundaries between family members are nebulous, and, as a result, family members may appear to be equally affected by the status of the patient. The care provided the patient may be sporadic or inconsistent because the family may be overwhelmed by the severity of the illness. Careful medical and psychosocial coordination between patient, family, staff, and, when appropriate, a drug treatment center, is necessary to maximize cooperation and to maintain quality care. Despite the level of frustration associated with this group of patients, dignified care is possible and attainable.

Intimacy and Sexuality

Advanced disease always affects sexuality and sexual functioning. Notwithstanding, the lack of libido and impaired sexual functioning are frequently overlooked or ignored as a concern of the patient. Open discussion of intimacy and sexuality with the team can actually result in enhancement of emotional vitality. In fact, an increase in intimacy can evolve as closeness is redefined and openly discussed. Patients' needs for intimacy and sexual activity must be examined and supported. A couple's expression of intimacy, even during terminal care, can create a sense of normalcy and relief in the midst of a highly traumatic course of medical events. As patients enter the terminal phase, these discussions require a high level of sensitivity. Most patients long to be touched and held, and it is not uncommon for spouses

or children to lie in bed with a dying patient to provide comfort and experience closeness or intimacy.

Dying at Home

While many patients and families describe a preference for death to occur in the comfort of their homes, this goal is not always attainable. Approximately 76–80% of patient deaths occur in medical institutions; only 10–14% of patients die in hospices, and the remaining 5–10% die in nursing homes or in patients' homes (61,62 and 63). The return to home, nursing homes, or hospices as the chosen places of death continues to increase, primarily as a result of the Medicare Hospice Benefit (64) and physician availability for home visits (65). A number of key psychosocial variables (table 54-2) may inhibit or prevent the occurrence of death in the home even with the highest level of supportive care or hospice services. Families must be carefully assessed and prepared for the death event. Key family members can be specifically questioned concerning their level of comfort or toleration for stressful events within the home. Preparations, including advance directives, wills, and do-not-resuscitate orders, should begin as early as possible to resolve all questions and informational needs that the family may possess. Typically, hospice services are only available in the home for a fraction of each day. Consequently, the patient's death will probably occur when the family is alone.

A family that wants to maintain a dying member at home despite complex needs may suddenly request that the patient die in the hospital. Reasons for rapid changes may be obvious and practical or may be irrational and unconscious. Either way, the resources and limitations of the family must be assessed and supported. Many terminally ill patients possess acute care needs (e.g., pain control, mental status changes, etc.), and admission may be warranted to provide brief respite for the family or to actually manage the death event.

When the Patient Dies

The final hours of the patient's life have significant meaning for the family and offer an opportunity for closure. The ritualistic need to be present at the exact moment of death can be very powerful for family members. The desire to be present for the death event is common, and for family members who are absent, significant regrets may result (66). Unexpected deaths occur in about 30% of patients; attempts to notify the family of the impending event is possible in 70% of cases (67).

Family members may require objective information concerning the cause of death, especially if the death was unexpected. Despite the terminal prognosis, many families need to understand why the patient died when he or she did. This information can mitigate the high level of distress and address any irrational concerns and fears associated with the death as it is happening.

Interactions with staff that occur immediately following the death can have a long-term effect. Emotional reactions of family members are expected, and crying, sobbing, and wailing are common. The therapeutic demands associated with the provision of terminal care challenges the health care professional to communicate with empathy while facilitating the initiation of essential tasks such as removal of the body and funeral arrangements. Families vary in their ability to receive information and emotional support during this time. The relationship between the family and the health care team influences how much of these preparations can be made prior to the death event and how much clinical intervention the family requires and can tolerate. Generally, families elect a spokesperson to provide and receive information but care must be taken to assess other members of the family. A follow-up meeting with the family by a social worker or nurse in the home can be very helpful to identify any family member who may be at risk for an abnormal grief response (68).

CONCLUSIONS

All patients and families possess a personal meaning of disease, prolonged illness, and death. These meanings are influenced over time by numerous factors. A clear understanding of these meanings, associated emotions, and their antecedents enhances the health care team's ability to provide care and anticipate potential problems. Information and education must be consistently available as the patient and family move across the disease continuum toward and post the death event (69).

Variables, such as cohesion, describe the quality and intensity of relationships within the family. High cohesion or enmeshed families lose more than a family member when the patient dies. For these families, part of their identity is also lost. Given their extreme level of dependence, these families may experience the death as catastrophic, which prevents the effective resolution of the loss. Chronic grief can exacerbate current psychological symptoms and influence health care practices. Bereavement follow-up among high-risk families is essential as a means to develop psychosocial prevention programs. The psychosocial obligation to the family does not end with the patient's death, and some families may require followup beyond the customary 1-year period. Given the intensity of the loss and the family's level of risk, grief must be monitored and resolved.

Ultimately, the role of the health care team is to create an environment with exquisite symptom management and honest and open communication (70). If these components are present, the opportunity exists to provide meaning to the death event. If this occurs, a sense of growth is possible for dying patients and family survivors.

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DISORDERS OF SEXUALITY AND REPRODUCTION

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The medical treatment of cancer patients has become increasingly effective during the past decades, extending lives and increasing survival. As a result the emotional and physical side effects of cancer treatment have gained increasing importance. Although the long-term, sexual side effects of cancer treatments have received considerable attention in clinical research during the past decade, potential infertility and its emotional cost have not been documented as thoroughly, perhaps in part because until recently there was no large cohort of long-term cancer survivors concerned with their own reproductive potential. Therefore, this newly emerging area of interest is to some extent a sign of more effective cancer treatments in younger populations.

After active treatment, survivors attempt to return to their previous daily routines. The challenge this represents for many cancer survivors is not trivial. Sexuality is one of the most complicated areas of functioning to regain. A diagnosis of cancer means having to face one's own mortality, possibly for the first time. The treatments are often painful, frightening, and intrusive and have the potential to erode one's sense of body integrity and body image. Memories of the illness and treatment together with their emotional aftereffects present a disruptive mix for sexual interest and functioning. These effects may continue long after active treatment is over and are “stirred” again at every routine follow-up visit.

Many cancer treatments interfere physiologically with some aspect of physical functioning, which also may impede an easy return to pretreatment life. These disruptive, long-term effects are not only those that directly affect sexual organs or gonads but also include other aspects of functioning that may interfere with the patient's sexual self-image, such as scars, a change in physique as a result of hormone treatment, ostomies, disfiguring surgery, and so on. Any change in appearance or functioning and any long-term treatment side effect can be a reminder of the illness and its treatment and may interfere with a sensuous, virile, and confident sexual self-image.

Changes in gender-role behavior resulting from the physical and emotional side effects of cancer surgery or treatment not only may impair the patient's sexual interest, but also affect the partner's perception of the patient as a sexual object. For both the patient and the patient's partner, it may be difficult to view each other from the same perspective that had previously drawn them to each other sexually. The patient may have become physically and emotionally dependent on the partner, who in return may have had to assume a nurturing, parenting role. After treatment ends, it may be impossible to return to the previous role distribution in the relationship. Both partners also are faced with the varying reactions of extended family, friends, and colleagues to the illness and subsequent difficulties. These reactions may range from affectionate support to angry withdrawal, adding to the psychosocial difficulty of the posttreatment period. Worries about the possibility of a recurrence, together with uncertainty about the future, heightened anxiety and depression, a sense of personal inadequacy, and diminished sense of control in either or both partners also can interfere seriously with the resumption of a sexual life (1,2 and 3).

Despite the consistently documented negative effects of cancer and cancer treatments on sexual functioning, cancer survivors' experiences with their bodies continue to be sexual in nature. Little has been done to identify the richness of patients' attempts to integrate their cancer experiences into a new sexual self-concept. Research in this area has been hampered, among other factors, by methodological issues including the need for innovative approaches to solicit and measure responses (4,5).

The psychosexual issues regarding the prospect of infertility in this population appear to be undocumented at this time. To face death and at the same time to surrender one's chance of living on in one's offspring must present a depressing, noxious combination for many of the young, childless patients beginning treatment. On a marital level, the issue of possible infertility undoubtedly has a long-term negative effect on the stability of the relationship as well as the need to renegotiate aspects of the implicit relationship contract. Unattached patients may not worry about possible loss of fertility in the early stages of diagnoses and treatment but still may feel damaged and limited in their capacity as a potential mate. Research in this area is urgently needed to alert the medical community to this issue and to develop strategies for helping these patients cope with this immense psychosocial stressor.

Although psychosocial causes are responsible for much of the sexual and procreative difficulty that survivors experience, physical causes are to some extent more easily researched and identified. Therefore, the vast majority of studies in this area focus on medically caused sexual and reproductive dysfunction. In the following sections, this literature is reviewed by disease site and systemic treatments.

SEXUAL AND REPRODUCTIVE SIDE EFFECTS OF CANCER TREATMENT IN WOMEN

Breast Cancer

Breast cancer patients may be the best researched group in terms of the sexual impact of treatment on sexual functioning. Partly because radical mastectomy had been the treatment of choice for all breast cancer patients, the effects of breast loss on women's sexual experience and life were researched early. In recent years, it has been widely accepted that comparable survival rates may be obtained in early breast cancer patients treated either with traditional surgical procedures (modified radical mastectomy) or with breast-conserving techniques combined with radiation and, increasingly, chemotherapy. The psychological and psychosexual outcomes of these two approaches have been compared in a number of studies. Although some studies report a tendency toward better preservation of body image and sexual functioning in patients who elect breast-conserving treatment (6,7,8,9 and 10), there is no conclusive evidence that these women also have better overall adjustment. Schover (11) questioned the frequently assumed connection between mutilating breast surgery and poor sexual adjustment posttreatment. She suggested that a woman's overall psychological health, relationship satisfaction, and premorbid sexual life appear to be far stronger predictors of postcancer sexual satisfaction than the extent of the damage to the breast and that even a less damaged sense of desirability and better preserved body image may have only a subtle impact on actual sexual functioning after surgery. It is also possible that age at the time of treatment plays a significant role in these patients' perception of quality of life. Wenzel et al. (12) found that immediately after treatment for breast cancer, younger women (younger than or equal to 50 years) reported significantly worse overall quality of life than the older women in their study. No significant differences in sexual dysfunction or body image were noted in this study.

In an effort to clarify the nature of women's response to lumpectomy, McCormick and coworkers (13) studied 74 women following lumpectomy and radiation and reported that 39% of the sexually active patients avoided the treated breast, 20% stated that their partner avoided it, and 48% noted breast discomfort during sexual activity; still, 90% indicated a high level of satisfaction with the results of their treatment.

The implications of breast reconstruction for the psychological adjustment of the mastectomy population is also beginning to receive attention. Rowland et al. (14) studied 83 women who had undergone reconstruction after modified radical mastectomy for early stage breast cancer and reported that these patients generally returned to premorbid levels of sexual satisfaction and comfort. The timing of the reconstructive surgery may be a relevant factor for these women. In a retrospective study of women who had undergone immediate breast reconstruction after breast cancer surgery, and women who had delayed breast reconstruction, Al-Ghazal et al.

(15) found significantly superior outcomes for women who had undergone breast reconstruction at the time of their initial surgery.

Although there is now a growing body of research dealing with the emotional and sexual consequences of surgery for early stage breast cancer, little is known about the effects of systemic regimens for breast cancer on sexual functioning. In a survey of 1098 women who had been diagnosed with breast cancer 1–5 years earlier and who had been treated with different adjuvant regimens, Ganz et al. (16) found that patients who had received chemotherapy seemed to experience a higher incidence of vaginal dryness and pain during intercourse, whereas women treated with tamoxifen reported a higher incidence of hot flashes, night sweats, and vaginal discharge. In a large survey of breast cancer survivors Meyerowitz et al. (17) found no significant differences between their subjects and age-matched healthy women on a standard measure of sexuality. However, women who were most likely to have reported negative impact on their sexuality from cancer treatment included women who had experienced changes in their hormonal status.

A further concern is posed by the large number of women now receiving hormonal treatment, especially tamoxifen, for long periods. The long-term side effects of these treatments are only now emerging slowly and require more research in the future. Research to date suggests that tamoxifen actually may produce estrogenic changes in the vaginal mucosa of postmenopausal women (18,19). However, its impact on symptomatic vaginal atrophy in these women is unknown (20).

Cancer of the Female Reproductive Organs

The incidence of sexual problems in women after gynecological cancer treatment ranges in various reports from 0% to virtually 100% (21). This reflects both the many methodologic difficulties of assessment in this field and the varied treatments for gynecological malignancies. These treatments range from laser surgery for cervical carcinoma *in situ* to total pelvic exenteration and vigorous chemotherapies for advanced gynecological tumors. The gynecological malignancies, with their obvious significance for sexual function, deserve comprehensive study to help women recover sexually as fully as possible (22). As Van de Wiel et al. (23) point out in their review of sexual function after cervical cancer treatment, many studies use frequency of intercourse as the sole indicator of the quality of sexual relations. This sheds little light on the true sexual status of the gynecological cancer survivor. Further refinements in research instruments and methodology hopefully will benefit this population. A review of the research in this area is also available in Berek and Andersen (24) and McCartney and Auchincloss (25).

Cervical Cancer

Cervical cancer is the fourth most common neoplasm in women, with 13,000 new cases of invasive disease diagnosed annually in the United States. Excluding *in situ* lesions, treatment consists of radical hysterectomy, radiation therapy, or a combination of both approaches. For almost two decades, researchers explored and compared the relative incidence of sexual dysfunction in women with cervical cancer after surgery or radiation (26,27 and 28). These studies indicate that at 6 months posttreatment, both surgery and radiation patients reported no significant changes in sexual functioning. At 1 year posttreatment, however, both populations reported decreased sexual interest and radiation patients reported significantly diminished sexual functioning with severe dyspareunia, postcoital bleeding, and pain on penetration. These studies highlight the difficulties posed for sexual recovery by pelvic irradiation for gynecological cancer. The sequelae of fibrosis, vaginal stenosis, and decreased lubrication (29) are likely to interfere with sexual function unless treated appropriately, promptly, and continuously with vaginal dilators, effective vaginal lubricants (e.g., Astroglide and others) and, in some cases, a hormonefree vaginal moisturizer such as Replens.

Total pelvic exenteration is a surgical procedure occasionally performed to excise advanced pelvic tumors *en bloc* in the absence of distant metastases. The surgery entails removal of the bladder, urethra, vagina, uterus, ovaries, and rectum; two ostomies are created. The treatment is such a serious challenge to both physical and emotional recovery that early clinical reports explored whether postoperative quality of life justified the continued use of so radical an approach (30,31). Some researchers have reported that construction of a neovagina combined with special support and counseling efforts offers an improved chance for sexual rehabilitation after surgery (32,33 and 34). At present, however, many questions remain regarding vaginal reconstruction. The long-term advantage to patient adjustment and satisfaction must be weighed against the risk of these procedures. The psychological and practical adjustments required by exenteration, which include body image, ostomy, and mortality concerns, also merit continued further study.

The impact of gynecological cancer on a woman's sexual self-esteem or sense of worth as a sexual partner remains an intuitively powerful yet little-studied factor in postcancer distress. Van de Wiel et al. (23) compared 11 women treated for cervical carcinoma with a group of nonpatient controls and found that although the frequency of sexual activity did not differ between the groups, the patients with cervical cancer valued sexual interactions significantly less and had a lower self-appraisal of themselves as sexual partners. Although the small populations studied and the retrospective nature of the work limit conclusions, this report marks a valuable effort to illuminate the subtler but far-reaching consequences of gynecological cancer for sexual well-being.

Endometrial and Ovarian Cancer

Endometrial cancer presents most commonly in postmenopausal women. Treatment consists of surgery, radiation therapy, chemotherapy, or a combination of modalities. Ovarian cancer presents in premenopausal and postmenopausal women; surgical evaluation and debulking are ordinarily the first step in treatment, followed by a chemotherapy regimen with a combination of agents. Only with the advent of chemotherapy for ovarian cancer has the previously dismal prognosis for this tumor improved markedly. Studies of the long-term implications of this illness for the survivor's sexual function have begun to appear (21,35,36). Compared with healthy controls, women with these cancers report lower frequency of sexual behaviors, lower levels of arousal, increased incidence of dyspareunia, and problems with body image.

The ovarian cancer patient faces the serial trauma of a serious cancer diagnosis, major pelvic surgery with resultant changes to the vagina, a demanding chemotherapy regimen, treatment-related onset of menopause in the premenopausal patient, and complete loss of fertility. The psychological, physical, and hormonal impact on sexual function in this population merits further careful study.

The endometrial cancer patient must often contend with radiation changes to the vagina and pelvis (37). Vaginal changes include fibrosis with resultant shortening and narrowing; reduced elasticity of the vaginal wall; and diminished lubrication, creating high risk of dyspareunia. As mentioned earlier, the consequences of radiation to the vagina may be avoided or alleviated by the regular use of vaginal dilators and sexual comfort can be improved by the use of appropriate lubricants, vaginal moisturizers, and intercourse positions. An important area for future inquiry is the implementation of patient support and education plans for women facing pelvic radiation, which may increase contact with health care providers and encourage crucial patient compliance with these strategies during the demanding months of treatment, especially during the first year posttreatment, as radiation changes evolve and produce physical and relationship distress.

Vulvar Cancer

Vulvar carcinoma is a rare tumor arising primarily in older women. In early stage disease, treatment may consist of wide local excision. In more advanced disease, the lesions are often multicentric and radical vulvectomy is performed, which entails removal of clitoris, labia minora and majora, and bilateral inguinal lymph node dissection. Postoperatively, patients may experience a high degree of complications, including wound infections and lymphedema of the lower extremities as well as introital stricture. Research attention has begun to focus on this population in recent years (31,38,39) and reports document that sexual dysfunction posttreatment for vulvar cancer is common and affects all phases of the sexual response cycle.

Sexual and Reproductive Implications of Systemic Cancer Treatments in Women

Sexual and reproductive consequences of surgery are obvious, occur at the time of treatment, and are usually permanent. In contrast, the side effects of radiation and chemotherapy may accumulate over time and may not be permanent. Premature menopause, which is a frequent longterm side effect of systemic cancer treatments, such as chemotherapy, hormone therapy, and pelvic irradiation, have implications for both sexual and reproductive functioning. Ovarian failure secondary to single-agent and combination chemotherapy has been documented (40). Alkylating agents appear to be the most notorious cause of ovarian failure in older women (aged 40 and older). Resulting symptoms include amenorrhea and menopausal symptoms, such as hot flashes, irritability, vaginal dryness, and atrophy of the vaginal epithelium. The treatment increases the likelihood of vaginitis, dyspareunia, and decreased sexual interest. Although some women recover normal ovarian functioning after treatment, premature menopause is the long-term outcome for many women. Aside from the specific drug regimen used, age is an important variable in this context, with older women more prone to loss of fertility and early menopause, particularly after treatment with larger, cumulative drug doses. In a study of women who received high dose chemotherapy for breast cancer with autologous bone marrow support, Winer et al. (41) found that even though overall quality of life after treatment was relatively high in this population 1 or more years after completion of treatment, problems with sexual functioning were common.

Gonadal dysfunction and infertility after radiation therapy are difficult to predict. The central location of the ovaries within the pelvis, close to major nodal areas, makes damage from radiation scatter and leakage likely. As with chemotherapy, radiation damage is dose-related, cumulative, and age-dependent. Loescher et al. (42) found that permanent infertility after 25 treatments of 500 Gy occurred in 60% of women aged 15–40 years and in 100% in women aged over 40. Because pelvic radiation interferes with the vasocongestive processes of female sexual arousal, vaginal lubrication also may be impaired, and dyspareunia and vaginitis may develop. Therefore, pelvic radiation may result in long-term adverse effects on female sexual functioning (43).

Radiation treatment is often combined with chemotherapy regimens. In such cases it is difficult to differentiate between toxicity incurred from radiation versus that due to the chemotherapeutic agent(s). Data from women who received combined radiation and chemotherapy for Hodgkin disease suggest that these combination treatments result in additive ovarian toxicity (44).

CANCER OF THE MALE REPRODUCTIVE ORGANS

Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in men. It affects mostly older men; 80% of all diagnoses are made in men aged 65 years and older. Men and their partners in this age group are often at a developmental stage dominated by losses: retirement, death of peers, and separation from adult children who move away. These losses may include diminished sexual activity secondary to sexual dysfunction that precedes the cancer diagnosis. Changes in sexual functioning due to normal aging are often compounded by age-related chronic diseases, such as hypertension, and their treatment. In a prospective study of 22 men with stage B or C prostate cancer, Schover and von Eschenbach (45) found that 23% reported painful ejaculation prior to therapy and 40% reported erectile difficulties. More recently, Zinreich et al. (46) reported that 63% of 43 patients (mean age, 67.7 years) with varying stages of prostate cancer had erectile dysfunction before undergoing any cancer treatment. Of these, 44% were never able to obtain an erection and 56% reported difficulty maintaining erections during intercourse. For many elderly couples, the man's erectile difficulty results in a complete cessation of sexual activity.

Treatment for early stage disease commonly consists of surgery or radiation therapy. In early stage prostate cancer, the advances in medical technology have meant gains for sexual functioning posttreatment. Quinlan et al. (47), in a case series of 500 men, reported an incidence of erectile dysfunction of 32% with nerve-sparing surgery techniques compared with 85% after radical prostatectomy. Recovery of erectile functioning is often slow, however, and may exceed 6 months in some patients (48)

Traditional radiation regimens for prostate cancer also may produce erectile dysfunction as a long-term side effect. Schover (49) found in a review of the literature that the generally estimated 50% of erectile dysfunction after definitive radiotherapy may be inflated. The actual incidence may lie between 14% and 46% of all cases. The mechanism believed to be responsible for the development of erectile dysfunction in radiation patients is vascular scarring, which may develop 6 months posttreatment or later. Helgason et al. (50) confirmed the general observation of increased incidence of erectile dysfunction in men treated with radical prostatectomy compared to men treated with external beam radiation.

Advanced-stage prostate cancer is commonly treated with testosterone deprivation, accomplished by bilateral orchiectomy or the administration of estrogen, flutamide, or luteinizing hormone-releasing hormone analogues. All these interventions produce sexual side effects, including loss of desire for sexual activity and impaired erectile functioning. Men undergoing hormone treatments also are confronted with body image issues, reduced energy levels, and hot flashes, which may contribute to the development of sexual problems.

Testicular Cancer

Unlike prostate cancer, testicular cancer typically affects young men. It is the most common cancer in men aged 17 to 34 in the United States. These men are confronted with a life-threatening disease at a life stage in which they are supposed to separate from their families of origin and find their own identity as an adult. The demands of the illness interfere with the developmental goals of this population and interfere with the young man's concept of himself as an independent, strong, and virile person.

In the past, treatment routinely included unilateral orchiectomy, retroperitoneal lymphadenectomy, and either chemotherapy for nonseminomatous tumors or radiation for seminomas (51). Men with metastatic seminomas may receive chemotherapy in addition to radiation. Despite the traumatic aspects of treatment for testicular cancer and the psychosocial issues faced by this group, survivors of the disease fare quite well as far as their long-term sexual outcomes are concerned. Studies document levels of decreased levels of sexual desire and erectile difficulties that are not significantly different from age-matched controls. Fertility issues due to retrograde ejaculation as a result of surgical damage to paraaortic sympathetic nervous system pathways are a prominent concern for men after retroperitoneal lymphadenectomy (52). Rieker et al. (53) found in a retrospective study of 223 testicular cancer survivors who were more than 1 year postdiagnosis that 30% experienced overall performance distress, 10% had erectile difficulties, and 6% were anorgasmic. Fossa et al. (54) surveyed 31 men postbilateral orchiectomy and found that despite difficulties in dosing androgen replacement therapies, most patients were psychologically and sexually well adjusted to their situation. More evidence that sexual outcomes in this population are strongly influenced by psychosexual factors comes from Arai et al. (55), who found in a study that included patients who had been on a surveillance protocol post surgery that these men reported the same extent and nature of sexual difficulty as men who had also been treated with chemotherapy or radiation.

Thus, fertility concerns relating to retrograde ejaculation and chemotherapy appear to be the most common sexual side effects of testicular cancer and may impair sexual quality of life for these patients (56,57). Despite the relative low incidence of reported sexual dysfunction in this group posttreatment sexual support seems to be warranted in this young population. They may experience problematic relationships because of persisting low-grade sexual dysfunction, which is treatable (58).

Sexual and Reproductive Implications of Systemic Cancer Treatments in Men

Testicular function in adult men is particularly susceptible to injury by chemotherapeutic agents. Affected are the germinal epithelium, the Leydig cells responsible for steroidogenesis (59), and the hypothalamic-pituitary-testicular axis (60). Dysfunction of the testis occurs shortly after initiation of treatment and can persist for months or years after function has returned to other tissues. Manifestations of toxicity are reduction in testicular volume, severe oligospermia or azoospermia, and infertility (61). The effects of the alkylating agents have been particularly well documented. For example, doses of chlorambucil below 400 mg cause reversible oligospermia, and cumulative doses in excess of 400 mg result in azoospermia and germinal aplasia (62). Low sperm count and elevated follicle-stimulating hormone levels are physiological indicators of germinal aplasia. The Sertoli cells are more resistant to chemotherapeutic agents and consequently, testosterone levels may remain within the normal range during and after treatment.

Combination chemotherapy regimens may have an even more disruptive effect on the germinal epithelium than treatment with a single agent. MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) results in irreversible germinal dysfunction in male lymphoma patients. However, other regimens that are equally efficacious cause germ cell aplasia in fewer patients many of whom experience the return of spermatogenesis with time (40). Chemotherapeutic agents are not known to affect the male sexual response cycle directly.

In contrast to the consequences of chemotherapeutic regimens on male reproductive capacity, which have been established for a number of antineoplastic agents, the effects of radiation therapy on sexual functioning and fertility have received little attention to date (43). The testis and both the germinal epithelium and the Leydig cells are very radiosensitive. Damage and recovery appear to be dose dependent. Doses as low as 150 cGy may result in a marked, if transient, suppression of sperm production. Disruption of sperm production increases with accelerating doses; at 2000 to 3000 cGy, recovery may take 3 years; at 4000 to 6000 cGy, approximately 5 years; and above 6000 cGy, sterility seems permanent (40). By affecting the vasocongestive mechanisms necessary for erectile functioning, pelvic radiation also may cause erectile dysfunction in men.

CANCER SITES IN BOTH SEXES

Bladder Cancer

Bladder cancer arises primarily in older men and women, who already may have experienced age-related changes in sexuality. Whereas treatment in the United States previously consisted of cystectomy for lesions of any stage, early bladder carcinoma *in situ* without infiltration may now be treated with local excision and bacille Calmette-Guérin.

In patients with invasive bladder cancer, cystectomy is still the treatment of choice. Recent advances in the development of nerve sparing cystectomies in men and women promise improved sexual functioning outcomes in both sexes (63). A common sexual side effect for men after radical cystectomy is erectile dysfunction resulting from transection of the nerves governing erection (64) and loss of ejaculation secondary to excision of the prostate at the time of surgery. Changes in the sensation of orgasm may ensue. Patient response to this loss is not well documented.

In women, cystectomy may result in a narrowed or shortened vagina, scarring, and numbness or loss of sensation, all of which may impair the excitement response. Further-more, removal of both ovaries during surgery causes premature menopause in premenopausal patients, which may lead to reduced vaginal lubrication and desire. The simultaneous creation of a stoma and external diversion of urine generates concerns about body image, odor, leakage, and spills and thus may contribute

to sexual avoidance and other difficulties (65). In recent years, continent cutaneous urinary diversion and orthotopic bladder substitution have become clinically accepted alternatives to ileal conduit diversion. The a priori assumption had been that postoperative quality of life would be better following these types of continent cutaneous diversions. However, although studies on the validity of this assumption have been hampered by a lack of consensus regarding methodology, follow-up studies do not seem to confirm any advantage in quality of life or sexual functioning in these patients (66).

Colorectal Cancer

Cancer of the colon and rectum is the second most common cancer in the United States; approximately 140,000 new cases are diagnosed annually, primarily in older men and women. Surgery remains the mainstay of treatment; resection of the tumor with pelvic lymphadenectomy may be followed by radiation, chemotherapy, or both. Pelvic lymphadenectomy may result in damage to the parasympathetic nervous system, causing erectile dysfunction, and to the sympathetic nervous system, causing retrograde or diminished ejaculation. Past studies have reported a varying incidence of these side effects after treatment (67,68 and 69). More recently Havenga and Welvaart (70) studied 26 men with rectosigmoid carcinoma, nine of whom were treated with abdominoperineal resection and 17 of whom were treated with low anterior resection. Only two of the patients with abdominoperineal resection returned to sexual activity, five had erectile dysfunction, and seven were anorgasmic. Patients who had low anterior resection reported less sexual dysfunction after surgery; 12 maintained sexual activity, and four reported either erectile dysfunction or anorgasmia. Further evidence that abdominoperineal resection produces significant sexual dysfunction was reported by Koukouras et al. (71), who studied 60 sexually active male patients with colorectal cancer who were treated with high anterior resection, low anterior resection, or abdominoperineal resection. Patients with the abdominoperineal resection had the highest incidence of sexual dysfunction; 65% became sexually inactive, 45% lost all erectile ability, and 50% reported absence of ejaculation. New surgery techniques to address primary rectal cancer promises to improve sexual outcomes for some of these patients. In a prospective study, Maas et al. (72) evaluated the sexual outcomes of operative procedures that combine pelvic nerve-preserving techniques with radical tumor resection to ensure optimal local tumor control with minimal bladder and sexual dysfunction. They found that the nerve-preserving technique results in low morbidity and good functional outcome. Impotence was related to sacrifice of the inferior hypogastric plexus and preservation of the superior hypogastric plexus was crucial for ejaculation.

Hojo et al. (73) described the use of a nerve-sparing approach to pelvic lymphadenectomy in 134 patients with advanced disease. They found that although bladder dysfunction was best prevented with a nerve-sparing procedure, preservation of sexual function in men is more difficult and requires a high degree of nerve preservation. This approach is therefore not advisable for patients with locally extensive disease.

In patients with early stage rectal cancer who are treated by amputation of the rectum alone, erectile dysfunction appears to be less prevalent, but problems with the orgasm phase persist (74). There is a glaring shortage of studies focusing on the sexual side effects of treatment for colorectal neoplasms in women.

After the creation of a colostomy, both men and women must contend with issues of changed body image and sensitivity about cleanliness, odor, and fear of accidents. Sutherland and coworkers' early studies (75) have remained clinically on target; they found that the sexual impact of the ostomy far exceeds the extent of physical handicap. Depression, anger, and fear of being repugnant are common emotional reactions postoperatively and may contribute to a pattern of sexual avoidance. The medical staff must anticipate these issues and offer support to patients, whose challenges include self-care of the ostomy, overcoming fears concerning changed appearance, and regaining physical self-esteem. Other patients who are farther along in this process may provide invaluable help to the recovering colorectal patient in this regard. Overall adjustment to the colostomy may take more than 1 year, as documented by Hurny and Holland (76).

Sexual response after colorectal surgery remains an insufficiently understood area, particularly in view of the current high prevalence of this tumor. For women particularly, the issues of sexual recovery after colorectal and bladder cancer remain too little explored. Nonetheless the impact of pelvic surgeries on the female excitement and orgasm responses, as well as the impact of the ostomy issues on desire, may be surmised to be great. The value of treatment interventions for sexual dysfunction in this population, including both penile prosthesis implantation and sexual counseling for the patient or couple, is also an appropriate area of study.

Other Cancers

Patients with less common tumors and those with common tumors that do not directly affect the organs of sexual response have received little or no research attention with regard to the sexual sequelae of their treatment. The diagnosis and treatment of all cancers have far-reaching psychological implications for the patient and family that lie beyond the scope of this review. These matters are covered comprehensively elsewhere (77). Some cancer treatments pose a particularly severe challenge to the recovery of normal selfesteem and restored body image; treatments involving limb amputations, marked facial and other appearance changes, or loss of normal phonation are examples. In a rare study of the sexual outcomes of patients with head and neck cancer, Monga et al. (78) found that although the majority of patients studied continued to be interested in sex, only 49% were satisfied with their sexual functioning after treatment. Older patients (65 years and older) reported more satisfaction with their sexual partner and current sexual functioning than younger patients, who also tended to have more advanced disease and lower performance status, and significantly poorer sexual functioning.

The simple passage of time does not heal all wounds. In the area of sexuality, it is not uncommon for problems to become more severe with time (79). The adjustment to cancer and its elements of disfigurement is by nature a slow process, and problems with adjustment and recovery, including those in the sexual and relationship arena, may often be more accessible to counseling by oncology mental health professionals during the first and second posttreatment year than at a later stage in cancer survivorship.

Cancers that require systemic treatment with chemotherapy, whole body irradiation, or bone marrow transplantation challenge the patient physically and emotionally more than most surgeries or radiation regimens. Treatments may be lengthy and arduous, depleting the patient of energy and causing severe side effects. Sexual functioning is clearly affected by many of these regimens. In recent years, the sexual concerns of female bone marrow transplant patients have received some research attention. Ovarian failure secondary to conditioning treatment with melphalan or cyclophosphamide and total body irradiation is associated with profound effects on sexual functioning, most commonly vaginal dryness, loss of desire for sexual activity, and difficulties with sexual intercourse (80). Ostroff et al. (81) found that standard regimens of hormone replacement therapy did not alleviate all sexual impairment experienced by women with treatment-related ovarian failure. In a study comparing bone marrow transplant survivors and a matched sample undergoing maintenance chemotherapy, Altmaier et al. (82) found that bone marrow transplant patients reported a higher incidence of sexual difficulties. Ostroff and Lesko (43) confirmed the prevalence of sexual dysfunction in bone marrow transplant survivors. Clearly, this population is at increased risk for sexual dysfunction and would benefit from further research attention.

Patients with Hodgkin's disease are now often successfully treated with aggressive chemotherapy. Treatment is associated with a high degree of infertility in both men (80–90%) and in women (50%) (82). The interrelationship in young cancer survivors between cancer treatment, loss of desire and sexual dysfunction, lost or impaired fertility, and relationship distress remains clinically inescapable but very little studied.

A group that also has received very little attention concerning the sexual and fertility related sequelae of cancer and its treatment are survivors of childhood cancers. Relander et al. (83) surveyed 77 adult male survivors of childhood malignancies. One-third of them had been treated for hematological cancers, one-third for central nervous system tumors, and one-third for other malignancies. They found that patients treated for tumors in the hypothalamic-pituitary region, with testicular irradiation, and those treated with high doses of alkylating agents suffered from severe gonadal and sexual dysfunction as adults. Puukko et al. (84) found in a survey of 31 survivors of childhood leukemia that although they did not differ from healthy, age-matched controls with regard to the frequency of sexual intercourse, their sexual identity was less well developed and they had more restrictive attitudes about sexuality and sexual pleasure. More research is needed to assess the long-term physical and emotional outcomes of these young patients with cancer.

PREVENTION AND MANAGEMENT OF SEXUAL AND REPRODUCTIVE DYSFUNCTION IN CANCER PATIENTS

Medical Strategies to Prevent and Manage Sexual and Reproductive Dysfunction

Efforts have been made to reduce sexual and reproductive morbidity by refining surgical and radiation therapies. Examples include the development of nerve-sparing surgical techniques to preserve erectile function after prostatectomy (85) and nerve-sparing retroperitoneal lymph node dissection (RPLND) for men with clinical stage I nonseminomatous testicular cancer to preserve emission and ejaculation. In some cases the effort to preserve ejaculatory function and avoid other treatment side effects in men with nonseminomatous tumors who do not evidence metastatic spread led to the use of unilateral orchiectomy followed by careful observation. A further example of the attempt to preserve quality of life is the strategy of offering observation as a treatment for nonmetastatic seminomatous testicular cancer instead of immediately proceeding with chemotherapy post-RPLND, thus preserving gonadal functioning. New, nerve-sparing techniques that involve preservation of the superior hypogastric plexus also may contribute to the preservation of ejaculatory functioning (86) in these men.

Similar attempts have been made to preserve sexual functioning in some treatments used for cancers in women. For example, wide local excision for vulvar cancer (38) and lumpectomy of breast tumors mark efforts on the part of surgeons to preserve sexual function and body image as much as possible without compromising treatment efficacy.

In both men and women, efforts to keep pelvic radiation doses to a therapeutically efficacious minimum may reduce the incidence of radiation-induced sterility and allow recovery of gonadal function. Radiation damage to gonads in men now may be reduced drastically by employing a new testicular shield that reduces scatter to about 10% of the patient's prescription dose. In women, oophoropexy (the surgical transposition of the ovaries to a midline position behind the uterus) reduces the ovarian exposure of women receiving pelvic radiation in about 50% of patients (87). These developments reflect the growing willingness of the oncology world to try to preserve and maintain sexual and reproductive function while providing appropriately aggressive cancer therapy.

Medical treatments for iatrogenic sexual dysfunction and infertility also have begun to be developed. Loss of emission and ejaculation is a frequent side effect of RPLND in men. Because most men undergoing this procedure are young (17 to 34), this loss is a serious concern. For men with adequate sperm production before sterilizing cancer treatment, cryobanking is usually advised. However, many patients present with suboptimal sperm before treatment. To secure a postthaw sample adequate for spousal insemination, more than 20 million sperm per milliliter with at least 40% progressive motility is generally required (40). Multiple ejaculates, if time permits, can increase the total of viable sperm for storage. For men after RPLND, antegrade ejaculation may return with time and, in some men, sympathomimetic drugs such as ephedrine or anticholinergic drugs, such as diphenhydramine or imipramine, may help to facilitate normal ejaculation. Electroejaculation is possible to harvest sperm in men who do not recover ejaculatory function (88). Recently, there have also been some encouraging medical developments to help patients overcome sexual difficulties. Particularly notable in this context is pharmacologic injection therapy for erectile dysfunction and ongoing research exploring the use of topical agents to promote erections in men with organic impotence.

Other interventions to help cancer patients overcome iatrogenic gonadal and sexual dysfunction focus on hormonal intervention. Hall and others (89) treated nine women with acquired hypogonadotropic hypogonadism after therapy for cranial tumors using a physiological replacement regimen of exogenous gonadotrophin-releasing hormone. This restored ovulation and fertility in 78% of the participants. Although the technology does not yet exist for the safe thawing of frozen ova, cryobanking of fertilized eggs (i.e., embryos) is possible. Several fertility centers now offer this option. Bone marrow transplant patients may be stimulated with hormonal therapy at the end of chemotherapy to stimulate ova for collection. The fertilized ova are frozen until later implantation in the patient or a surrogate mother. This procedure is experimental and controversial (43) and carries the potential burden for the father to decide how to proceed if the spouse's therapy is not successful.

Women who undergo premature menopause after cancer treatment need medical intervention to alleviate menopausal symptoms and prevent atherosclerosis, hypertension, cardiovascular accidents, and osteoporosis. Unless an estrogen-sensitive tumor was involved, hormonal replacement should be considered (90). Wren (91) argued that hormone replacement may be feasible in most women after genital tract cancer. In his view, estrogen/progestogen regimens will not affect malignant cell growth in vulvar and vaginal cancer as well as squamous cell carcinoma of the cervix. Although the endometrium and the ovary contain hormone receptors that may respond to estrogen by increased growth factor production, a large number of women with these cancers were cured by the initial treatment and would benefit from hormone replacement without risk of stimulating cancer growth. Women who were not cured may benefit from treatment with progestogens alone or estrogen and progesterone in combination to relieve any discomfort caused by estrogen deficiency.

Aside from estrogen replacement therapy, nonhormonal medications, such as clonidine, methyldopa, and betablockers, may be used to control hot flashes (92). Emotional instability also may be addressed with serotonin selective reuptake inhibitors such as fluoxetine or sertraline. Topical solutions to counteract reduced lubrication and changes of the vaginal lining include Replens, vitamin E oil, Chaste berry, 1–2% testosterone cream, and limited doses of estrogen cream or Vagifem (93). Androgen treatment may be indicated in women with reduced bioavailable androgen levels after chemotherapy (94) and may improve sexual interest.

Psychosocial Prevention and Intervention for Sexual Difficulties

Although efforts are under way to prevent and alleviate adverse sexual and reproductive side effects of cancer treatments medically, severe physical and emotional damage can occur nonetheless. Even patients whose treatments did not affect sexual end organs report being impaired in their sexual enjoyment after cancer treatment. Indeed, impaired sexual functioning during or after cancer treatment can occur regardless of the specific physiological changes that have taken place. The sexual response cycle (desire, arousal, and orgasm) is a complex process that may be disrupted by a wide range of factors both physiological and psychological.

Sexual response during and after cancer treatment is vulnerable to the impact of the cancer itself, medical treatment side effects, other medical problems, medications, pain, depression, anxiety, partner response, and subtler psychological effects, such as changed body image and belief in cancer myths. Cancer patients must face their own mortality, undergo uncomfortable, sometimes lengthy, or disfiguring treatments, and deal with the effect of their illness on spouse, family, and work. An understandable consequence of this process can be loss of sexual desire and impaired sexual response. Von Eschenbach and Schover (95) found that the most frequent sexual side effect reported by men with cancer is erectile dysfunction, whereas women are more likely to lose interest in sex altogether. Loss or impairment of sexual desire may be triggered by the trauma of diagnosis and treatment, which interferes with the patient's perception of himself or herself as a sexual person. There may be concerns about one's attractiveness and the partner's reaction that contribute to an overall withdrawal from sexual activity. Concerns about sexual functioning may contribute to sexual avoidance even if sexual desire per se is not impaired.

Although inhibited sexual desire, sexual avoidance, and erectile dysfunction may be the most frequently observed sexual difficulties in this context, any sexual dysfunction may be caused by the patient's and the partner of the patient's reaction to the trauma of the experience. Little has been reported on how ethnic differences in sexual socialization and attitudes affect sexual outcomes of cancer treatments. Most populations studied at major cancer centers are predominantly white, and there often are not enough members of different backgrounds to enable researchers to compare subgroups along these lines. Wyatt et al. (96) compared 147 African-American and white breast cancer survivors and found that even though both groups in their study were from very similar sociodemographic backgrounds, African-American women were significantly less likely to be comfortable with and practice oral sex and any self-touching/masturbation than their white counterparts. Also white women were much more likely to report that breast cancer had a negative impact on their sex lives. Ethnic differences in survivor groups deserve much more attention to enable treatment providers to deliver psychosexual support in an optimal fashion to all patient groups.

The medical team often fails to help prevent development of sexual dysfunction by not addressing the topic with the patient. This may be due to a number of factors such as discomfort with the topic or a concern about appearing intrusive or presumptuous. When the patients are elderly, young, single, widowed, or homosexual, sexual concerns appear to be particularly difficult to address (58). All too often, sexuality is viewed as being a concern only for men and women who are sexually active within a committed relationship. Every patient, regardless of current level of sexual activity, has a perception of himself or herself as a sexual being and is invested in knowing that he or she can function sexually even if not pursuing any sexual relationships at the moment. Often, the medical staff waits for the patient to open the topic and concludes that there is no interest in sexual issues if the patient remains silent. Vincent et al. (26) found that 80% of patients receiving cancer treatment were interested in more information about sex, although 75% said they would not initiate conversation about it with their doctor. Cancer patients often feel they should be glad to be alive. Asking about sexual concerns may seem ungrateful and frivolous. If physicians and nurses initiate communication about sexual side effects of proposed treatments at the time of treatment decisions, they signal to the patient that sexual functioning is a legitimate concern that can be addressed.

Privacy and confidentiality are crucial prerequisites for discussing sexual concerns with patients. Sexual matters cannot be discussed productively during rounds, when several staff members are present or when a roommate is within earshot. Under such conditions, the clinician is likely to encounter vague responses and little enthusiasm for the topic. Assessment of the patient's sexual status and history at the time of treatment decision provides the crucial basis for members of the medical team to give appropriate support and information about the possible impact of treatment options on sexual functioning. It also signals to the patient that sexual concerns are understood to be an integral component of patients' quality of life. The time of diagnosis and treatment decision is a stressful one for the patient and his or her partner, and sexual concerns are not likely to be in the forefront of their minds. However, sexual functioning needs to be addressed from the start to support the patient in the struggle to adjust to the impact of cancer treatment on self-image and functioning. Clear and detailed information enables patients and their partners to anticipate problems and prepare for them. The nursing staff in particular can be instrumental in helping patients and their partners deal with both emotional and physical side effects by explaining the physiology involved, normalizing the experience, and giving pragmatic advice and coping strategies. The timing of these interventions is determined by the situation. Certainly in emotional or medical crisis situations, such as when a relapse of the cancer is discovered, it is not helpful for the patient to be asked about sexual matters. Sexual advice is best received when it specifically addresses the problems with which the patient and his or her partner are currently struggling.

At the time of treatment decision, the patient needs to know about the sexual and reproductive issues that may arise as a result of the treatment. Patients also need reassurance that help is available should sexual difficulties occur. As treatment proceeds and patients are seen for follow-up visits, the sexual status should be assessed by asking openended questions like, “How are things going in your relationship?” and “How are things sexually?” As patients express difficulty, it is easy for the caregiver to normalize the experience of the patient and to offer specific advice on how to improve matters sexually.

Because any change in appearance and functioning may have sexual consequences, the medical staff should consider the potential sexual implications of all treatments offered to the patient and address them with all patients. A good resource for both staff and patients is a pair of booklets published by the American Cancer Society that address sexual concerns of male and female patients after cancer treatment. The booklets are lucid, practical, and informative about both sexual side effects and strategies to deal with them (97). If patients continue to experience sexual difficulty after cancer treatment, referral to a sex therapist for careful evaluation and treatment is indicated.

Often, a short course of sexual counseling suffices to facilitate better adaptation and functioning, particularly for patients who had a satisfactory sex life before the cancer diagnosis. Sex therapy with cancer patients is geared to address the specific difficulty expressed by the patient and the patient's partner. Sexual attitudes and fears are explored, and frequently physical exercises are prescribed to do at home. These exercises are designed to reintroduce sexual activity slowly. Usually these exercises follow a graded approach, beginning with general physical pleasuring and gradually becoming more sexually focused. This approach is particularly helpful to patients who have a great deal of performance anxiety, who avoid sexual activity for fear of being unable to complete it, whose confidence in their ability to function is shaken, and who feel unattractive and shy about how their bodies were affected by cancer treatment. Similarly, partners can be traumatized by the experiences they had in the course of the treatment and also may benefit from such exercises.

SUMMARY

The focus of the available literature is primarily on the incidence of sexual and gonadal dysfunction after cancer treatment. Very few authors compare their population with normal age-matched controls. Considering the high incidence of sexual difficulty in the general population (98), such comparisons might reveal how very successfully many cancer survivors are able to integrate sexual side effects and continue some sexual life despite the impairing physical and emotional side effects of their treatments. New medical strategies aim at prevention and amelioration of sexual side effects and infertility. Comprehensive psychosexual support during and after treatment promises to further aid patients and their partners in minimizing negative sexual outcomes. Sexual side effects in particular can be addressed in brief sexual counseling or therapy. Informing the patient of possible side effects before treatment makes early intervention of psychosexual difficulties possible. Psychosocial aspects of fertility concerns of the cancer patient during active treatment and as a survivor have received little attention so far, possibly because of previous experience, when long-term survival of young patients was rare. With advancing technology in cancer treatment, this cohort of long-term survivors is likely to grow and requires an adequate response to these medical and psychosocial needs.

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HOME CARE

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INTENSIVE CARE OF HOME CARE

Since the mid-1980s, there has been a major shift in home health care. In the United States this shift was caused originally by the prospective system; it has been sustained by current trends toward managed care. Long hospital stays have been replaced by early discharges and the shifting of the burden of care to the home. The intensity of care for these home care patients has also changed because of the demographics of both patients and caregivers. Home care nurses and family caregivers have been charged with managing patients with complex and highly technical treatment plans. Home care is characterized by intensive management of symptoms and by needs for supportive care of both the patient and the family caregivers who assume the burdens of cancer and its treatment (1,2,3,4,5,6 and 7).

Complexities of Home Care in the 1990s

Until recently the study of symptom management has been largely confined to major symptoms, such as cancer pain, and to acute care settings. Recent studies have focused on the special needs of patients in other settings, including the nursing home (8,9,10,11,12 and 13), the hospice (14,15,16,17,18 and 19), and the home (2,20,21 and 22). Several factors can influence pain management in these settings. Heavy reliance on family members, access to diagnostic facilities, and, often, limited pharmacy services can influence the effectiveness of pain and symptom management at home.

It may be assumed that comfort is enhanced in home care, as the home environment has been considered preferable to institutional settings. Indeed, patients, families, and health care professionals often elect care at home because they assume that patients are more comfortable there. Research has not confirmed this perspective—at least in the case of pain management—and has demonstrated that treatment may not be substantially better at home (20,23). As researchers have extended studies into the home care setting, barriers have been described that actually hinder pain management in the home, including patient's and family's fears of addiction, failure of the patient to report pain, and limited access to needed services (24,25,26,27,28,29 and 30). These facts emphasize that fulfilling the patient's preference to be at home may not necessarily result in effective symptom management.

Symptom management is different at home than in the hospital or other institutional setting (20). Hospitals typically provide technical equipment and services for acutely ill patients. For patients with complex problems, inpatient care often includes a variety of aggressive or invasive strategies for diagnosis and definitive treatment of the underlying conditions. Home care, by contrast, relies heavily on low-tech strategies, concentrating mostly on symptom management. The overall effectiveness of these different strategies at home in comparison with hospitals remains difficult to analyze.

Cancer as a Family Experience

Cancer and other life-threatening illnesses, such as AIDS, are generally recognized as affecting the entire family unit rather than a single individual. The recent shift in health care, with movement toward home care as the predominant setting, emphasizes the importance of family involvement in the total care needs of the patient. It is indeed remarkable that care which only a decade ago was reserved for intensive care units by specially trained registered nurses is now delegated to family caregivers in the home environment who have had little or no preparation to assume both the physical and emotional demands of illness (31,32,33,34,35,36,37,38,39,40,41 and 42). Home care has advanced from low-tech care, focused on follow-up for patients discharged from hospitals, into its current status as the setting for active treatments, including chemotherapy, intravenous fluid administration, blood transfusion, complex wound care, and many other technical procedures. Recent literature has acknowledged the intense demands of family caregiving at home largely in the areas of technical care, acquisition of skills, and provision of intense, 24-hour physical caregiving. Less emphasis has been placed on the emotional burdens of assuming responsibilities for the patient's well-being or peaceful death in the home (43,44,45 and 46).

The home environment can be viewed as a delicate balance. At one end of the spectrum are the many demands that the home care environment offers that, if out of balance, can result in intense burdens for family caregivers and compromised care for patients. At the other end are the many benefits of home care. The home care environment potentially can offer the patient improved physical comfort, the psychological comfort of familiar surroundings, an opportunity for healing of relationships, and the ability for patients and families to benefit from the compassion of giving and receiving comfort care and a shared transition from life to death (15,45,47,48).

Another significant trend has been the use of home as the setting of care. In the late 1970s and early 1980s, health care professionals generally made the decision whether to discharge a patient to the home or to offer an extended stay in an inpatient setting based on patient or family preferences. The decade of the 1990s transformed home care as the primary setting of active treatment as well as palliative care. Very important, however, has been the diminished choice on the part of patients and families primarily due to changes in the health care system (38,49,50). Although some patients and families have volitionally chosen home care, others have had care relegated to the home setting due to health care system or hospital determinants.

The potential benefits of home care also have been threatened in the United States by the managed care movement. It is now common practice for patients to be discharged from acute care stays with a limited number or duration of home care visits, often limited to only a few nursing visits or a duration of care of only a few weeks. Subsequent care then is provided only by the patient and family with no professional support.

The outcomes of home care may often be best evaluated by the effects on family caregivers following the death of the patient and during bereavement. Hospice providers have long recognized that positive experiences with caregiving in the home result in positive bereavement and adaptation by family members after the patient's death. Feelings of inadequacy in providing home care, patient complications, and deaths that are less optimal than anticipated can result not only in the patient's diminished quality of life or quality of death, but also in long-term consequences for the family. Home care then is best viewed as not merely care provided to a single individual in the home environment but rather as a family experience in which every aspect of care provided to the patient or the provision of care by the family caregiver will impact the others (51,52,53,54 and 55).

Public Denial of Death and Influence on Care

Much literature has addressed the social need to deny death and the reluctance of individuals in society to accept death and dying amidst a health care system focused on cure. Efforts by the hospice movement, the social influences of AIDS, the prevalence of cancer, and other factors have in many ways made our society confront the reality of death in recent years. In an effort to diminish societal denial of death and heighten awareness of the growing end-of-life movement, the well-known documentary reporter Bill Moyers produced a 4-part series for public television that aired in fall 2000. Through his years of work in preparing “On Our Own Terms: Dying in America,” Moyers sought to address myriad aspects of how individuals, families, and the health care systems view and manage death in the United States. This was the first time in modern U.S. history that such a well-known media personality devoted such substantial effort to examining the societal views toward end-of-life. For professionals in the end-of-life movement, this represented a major coup in overcoming societal silence, denial, and aversion to such a critical stage in life.

In the 1990s, several other programs were developed in the United States to address the need for increased research, professional education, and advocacy in end-of-life care, including aspects of home care, hospice, and community involvement. The Project on Death in America was established by the Open Society Institute through a grant from the Soros Foundation, one of the wealthiest philanthropic foundations in the United States. Interestingly enough, the benefactor recognized the incredible dearth of resources and training in caring for those at the end of life. Therefore, a major portion of the budget is appropriated toward Project on Death in America programs addressing aspects of end-of-life care in various professional fields, including medicine, nursing, social work, chaplaincy, and other social service fields. Efforts in training and research are intended to encompass a wide breadth of topics, including home care and caregiver issues, factors influencing care, and neglected areas such as how correctional systems manage pain and symptoms in incarcerated terminally ill persons.

Another organization emerged in the 1990s with the expressed purpose of addressing public policy and advocacy issues related to end-of-life care, including home care. Americans for Better Care of the Dying (ABCD), based in Washington, D.C., is involved in policy analysis, lobbying, and educating lawmakers as to the under-allocation of funds for necessary services for those entering the final stages of life. Ironically, the growing crisis in home care funding and services actually spawned the creation of organizations such as ABCD. At the end of the twentieth century, lawmakers were beginning to take notice while society as a whole seemed to maintain its denial of the staggering impact of caregiving and death on families and society.

These efforts at examining the end of life as a natural life stage have been balanced by intense media attention on new potentially curative therapies, such as gene therapy, biomedical engineering, and advanced technologies. This attention encourages continuation of the death-denying society. Health care providers should recognize that for many family caregivers and patients, the death that they are now witnessing is perhaps their first personal encounter with the termination of life. Family caregivers struggle with the sanctity of life and denial of death just as do health care professionals and society at large. However, the profound experience of dying, or of caring for a loved one who is dying, transcends all aspects of home care. This experience has been described as an all-encompassing aspect of the clinical care of the terminally ill patient at home (38,56,57 and 58).

Physical and Psychosocial Issues

The needs of patients and family caregivers in home care span the domains of quality of life, as depicted in Figure 56-1. Home care needs most often involve physical needs, such as management of pain and other symptoms, and treatment of the side effects associated with treatment of the disease. Nutritional needs, sleep disturbance, fatigue, incontinence, and other physical aspects of disease and treatment are common priorities of home care. In fact the area of physical well-being and symptom management has been the focus of home care and also is the area with the greatest scientific basis for the practice of care in the home (59).

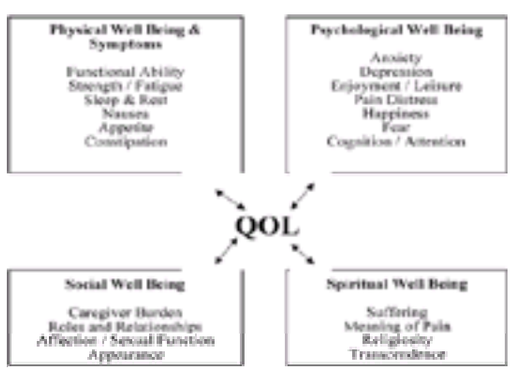

FIGURE 56-1. Dimensions of quality of life (QOL).

Psychological well-being is predicated on pharmacological management of symptoms, such as anxiety and depression, as well as counseling to address issues such as fears, loss of control, and the many other psychological demands of lifethreatening illness (60,61,62,63 and 64). Similar to psychological needs are the patient's social needs, such as the ability to maintain appearance and normal roles and relationships, and family issues such as financial concerns. The ability to meet psychological and social needs is more difficult outside palliative care programs, in which there is limited access to social workers, clinical psychologists, and other support personnel (65,66,67,68 and 69).

Spiritual well-being presents perhaps the greatest challenge in home care. In the institutional setting, such as the inpatient hospital, chaplaincy services may be more available. Yet it is during the advanced stages of illness, when care takes place in the home, that spiritual needs, like psychosocial needs, may become more prominent (70,71 and 72). This issue emphasizes the importance of psychosocial and spiritual assessment to determine unmet needs.

Innovative home care programs have begun to incorporate volunteer programs in order to meet the demands that simply will not be addressed in traditional home care services or those for which reimbursement is not possible. As a model example, the City of Hope National Medical Center has recently instituted a program in cooperation with the community Interfaith Council of Churches to begin providing intensive volunteer support for respite care and other services in order to enhance the current services provided in home care.

In addition, in recognition of the importance of community and volunteer involvement in home care and end-of-life care, the Robert Wood Johnson Foundation developed a funding program in 1999 through the Mid-west Bioethics Center to support partnerships that comprise community-based organizations and state government agencies aimed at enhancing collaborative efforts in the area of end-of-life care. Several of the recipients of the Community-State Partnership grants created innovative programs to incorporate faith-based organizations in training community and family members in home care aspects. The programs were established to coincide with the efforts of the Moyers series, “On Our Own Terms.” The longitudinal effect of the Moyers program coupled with the nationwide Robert Wood Johnson Foundation projects will remain to be seen. However, initial results of such efforts have evidenced a steady increase in the professional and societal end-of-life movement, with increased attention to the importance of home care, the needs of caregivers, and the lack of funding allocation for much needed services.

CHALLENGES TO SYMPTOM MANAGEMENT AT HOME

There are at present many uncertainties about the future of the health care system in the United States and in virtually all countries. A certainty, however, is that care continues to shift into the outpatient and home care environment. Thus it is patients and families who will assume the majority of care in the future. One of the greatest challenges in this area derives from demographical and social influences such as the impact of a steadily aging population of patients with multiple chronic illnesses. Care of the cancer patient at home becomes far more difficult when the patient is 80 years old and also has concomitant illnesses such as cardiac disease, hypertension, and diabetes, with their associated medications and treatments (73,74,75,76 and 77). There is still limited attention focused on the special care needs of the geriatric population at home and that of their caregivers, who are often elderly children (54). Expanded efforts in attending to complex needs of the aging will need to be adopted, especially given the growing percentage of population over the age of 65.

An equal challenge rests in the demographics of family caregivers in the home. Research has revealed that approximately 70% of caregiving is provided by elderly spouses in the home and an additional 20% is provided by daughters or daughters-in-law, who are often balancing full-time employment as well as the demands of their own families while providing intensive care to their loved ones (38,78,79,80,81 and 82).

One of the most challenging aspects of home care will be the future impact of managed care and similar factors influencing the types and extent of care to be provided

in the home. Factors, such as limitations in the types of services available, the frequencies of visits, and the duration for which this care can continue, will make home care extremely challenging. In essence, as the intensity of needs is increasing, the available resources in home care are diminishing.

Involvement of Family Caregivers in Medications

A primary task of home care related to cancer and other terminal illness is management of medications. It is enlightening to realize that home care nurses and other professionals assume similar responsibilities in other settings only after formal courses in pharmacology and with support available from colleagues, pharmacists, and physicians reached by direct access. This is particularly true in oncology, where symptom management is often either accomplished on an as-needed basis for symptoms, such as nausea or anxiety, or with necessary titration of around-the-clock dosing of medication such as analgesics (58,83).

Management of medications is important not only to preserve the patient's comfort but also to diminish the burden on the family and avoid costly complications such as repeat hospitalizations when medications are not effectively used (84). Patients and family caregivers often do not have the necessary knowledge to judge indications for administration of medications or the delicate issues involved with titration or the side effects of medications. Health care providers can make a valuable contribution to the care of patients at home by insuring that medication schedules are made as simple as possible using single agents rather than multiple drugs, and maintaining the simplest possible routes of administration and dosage schedules. Patients require assistance with important decisions regarding the use and titration of medications and practical techniques such as written dosage schedules, use of self-care logs, and provision of guidelines to help in medication choices. Table 56-1 includes examples of the types of decisions patients and families have reported in the use of pain medications at home. This illustrates the practical dosing decisions and the intense dilemmas patients and families may face in trying to seek relief of symptoms while avoiding the hazards of overmedication. Patients and families require information as well as support in their decisions regarding medications and treatments.

Deciding what to give "I am the 'pill pusher.' I have to assess intensity, mix meds, and try to find the right combo." Deciding when to give "Totally, I regulate it. I can tell by the look on her face when she needs more pain medicine." "I wonder about the time—whether to give it sooner or later." Night duty "I set my alarm to get up and get his meds." "Dad gives Mom the medications she's taking. He sets the alarm during the night." Reminding/encouraging "She doesn't like to take them, so I encourage her." "My mother has been reluctant to get involved in taking drugs for pain. I have tried to encourage her to take the drugs." "My role has been more of an emotional support rather than one of dispensing any drugs." Keeping records "I write down what time it is and how many pills I give." Fear of addiction "I try to control pills. He's popping them before it's time. He's angry . . . was he liking them too much? The prescription said every 4 hours, but I would try to hold off if he was crying at 3 hours for 15 minutes. I kept them in my drawer after I found he was popping them." "I know he needs the controlled drugs, but I hate to see him take them. So I don't remind him. He knows when he has pain. The only time I talk to him is when I think he has had too much medication." Doing everything "I do everything for her—give her the medications, et cetera." "I administer the pills. I do everything for him."
Adapted from Ferrell BR, Rhiner M, Cohen MZ, et al. Pain as a metaphor for illness. Part II: Impact of cancer pain on family caregivers. Oncol Nurs Forum. 1991; 18(6):1135–1142, with permission.

TABLE 56-1. THE CAREGIVER'S ROLE IN THE ADMINISTRATION OF PAIN MEDICATIONS

Other Concerns of Family Caregivers

An exploratory study investigated the experience of managing pain in the home from the perspectives of the patient, the primary family caregiver, and the home care nurse (83). In particular, the decisions and ethical conflicts encountered by members of ten patient-caregiver-nurse triads were studied. The subjects reported that the use of medications prompted the majority of the decisions and provoked most of the conflicts. However, decisions related to assessment, the future, and how to live with pain were identified as well. The subjects also identified other areas that created conflict such as spiritual and theological issues, determining when to tell the truth, and interpersonal relationships. Similar findings emphasizing the importance of information and support for family caregivers have been reported by other investigators (32,33,43,44,45,50,85,86).

An additional burden of family caregiving, often neglected, is the costs assumed by patients and family caregivers themselves related to pain management and home care (84,85,86,87,88 and 89). Families incur significant expenses related to home care in advanced disease, much of which is not reimbursed. Costs include direct expenses, such as medications, as well as extensive indirect costs such as loss of wages (38,39,88). Most of the cost savings to third-party payors have resulted in increased costs assumed by patients and families.

Cultural Considerations of Home Care

The increase in multiculturalism in the United States has added another dimension to the complexity of health care provision as well as coverage. Language barriers, cultural traditions, and religious beliefs create the need for increased sensitivity and knowledge on the part of health care professionals. No longer is health care—or home care—merely for English-speaking, Anglo-Saxon, Judeo-Christian patients and families (90). These facts present additional challenges when considering assessment of pain and symptoms as well as issues related to beliefs about death in various cultures (91,92). Assessment and treatment are complicated by cultural factors, and health care providers along with researchers seek ways to understand and accomplish a nonbiased medium from which to practice (93,94). Likewise, health care providers may be caught by the demands for individualized care in the midst of a growing multicultural society (95).

Some researchers argue that efforts to make all care and assessments standard without considerations of multicultural factors may actually increase health care costs (93). By taking into account these issues, health care providers assess the patient holistically. This approach may incorporate family and community resources as aids to planning culturally sensitive and appropriate care (96). While this may seem like a logical necessity, it has the risk of presenting even more demands and obstacles to an already overburdened home care system.

Notably, in many non-Anglo communities, it is tacitly acknowledged as a “duty” in the culture that the burden of much health care automatically shifts to the extended family. In theory this increases the number of caregivers, but it does not increase the certainty of training, understanding or efficacy of home care. In such environments, familiarity with one's ethnic, religious, or cultural beliefs—especially with respect to terminal care—is best appropriated within a person's respective community. Not only is this true for the patient but also for the surviving family and community. It may justify transcultural home care.

Benefits of Care at Home

A primary benefit of home care—its cost—has led to its growth. Care at home can significantly decrease the costs of care throughout the entire illness, from outpatient diagnostic procedures to active treatments, such as the administration of chemotherapy or blood products, to terminal care. Work at the City of Hope National Medical Center has demonstrated the significant cost reductions in comparing inpatient costs with those of home care (87). In this setting the potential cost savings of effective home care was shown to partly involve a reduction in unnecessary readmission for controlled symptoms. Work by Grant and Ferrell initially documented a cost of $5.1 million for the years 1989 to 1990 related to admissions for uncontrolled pain by this institution. Follow-up analysis for the subsequent years of 1991 to 1993 has demonstrated initial cost savings to the institution of $2.7 million in reduced admissions costs because of efforts to improve the quality of pain management (84).

Home Care of Children

Most literature regarding home care has focused on the care of adults. The care of children is often perceived to be less demanding or even normal as families are usually expected to provide such pediatric home care. On the contrary such care is quite demanding because of the characteristics of the ill child, the parents, the siblings, and the extended family. Recent studies have explored the experience of parents in caring for a child with pain. These studies added a dimension to the previous research related to families and pain and also described the decisions and conflicts in pain management for children (97,98,99 and 100).

Parents of pediatric cancer patients in pain often reported that their health care team did not take their child's pain seriously and did not provide adequate analgesia to relieve the pain (97). This is consistent with recent literature describing the inadequate assessment and management of pediatric cancer pain (101). However, when specialized pain teams were involved, they were better able to relieve not only the child's pain but the parents' emotional suffering as well. The parents' role in decision making varied from allowing the child to have control whenever possible regarding his or her treatment to personally administering nondrug methods of pain relief that temporarily alleviated both the child's pain and the parents' feelings of helplessness.

SUPPORTING FAMILY CAREGIVERS IN HOME CARE

The literature consistently supports the importance of family members during advanced illness. The caregiver's own health, attitudes, and knowledge have a profound

effect on the successful management of the patient's symptoms. This is especially important in the care of terminal cancer patients at home (102,103).

The control of chronic pain remains a perplexing problem that may have important implications for stress experienced by the caregiver. Increased anxiety, depression, marital and family conflicts, embarrassment, guilt, resentment, low morale, and severe emotional and physical exhaustion are commonly reported by distressed caregivers (33,42,43,44 and 45,50,104,105 and 106). Studies have revealed an overall marked decrease in dimensions of caregiver quality of life, which are particularly prevalent when the patient has unmanaged pain and symptoms (107). Indeed pain management may present caregivers with unique kinds of stress. For example, pain management often requires drugs that must be monitored carefully to achieve maximum pain control safely with minimum side effects. Newer, high-tech pain strategies, such as infusion pumps and chronic spinal infusions, also require the caregivers to have special knowledge and skills. The areas of greatest burden for caregivers in the management of pain include demands on time, emotional adjustment, distressing symptoms, work adjustment, sleep adjustment, and family and relationship adjustments.

Studies of family factors influencing pain management among cancer patients at home, made by this author and colleagues, suggest that caregivers need education and support to cope with many of these issues (20,23,37,53,54). These unanswered questions may lead to increased anxiety, stress, and overall burden on the caregiver that in turn may translate into inadequate pain management. The need for education and support for caregivers cannot be overemphasized in the management of pain in the home. Other researchers have asserted that identification of psychological needs of caregivers early in the home care process helps to form the basis for interventions to improve the long-term psychological outcome and bereavement after the death of their loved one (55).

As an advocate of the ethical issues facing family caregivers, Callahan (66) has been a champion of family caregivers and the struggles they face. Callahan has questioned the obligations of family caregivers when heroic, extraordinary care is needed. Improved social support from government agencies as well as a sensitive, responsive society that rewards the heroic efforts of family caregiving is required given the current demands on families. Yet such social recognition and value is often not present (66).

Jennings and colleagues (32) have discussed the ethical challenges the individual, family members, and society as a whole face as a result of the homebound chronically ill. Management of the chronically ill in the home results in social withdrawal and isolation, transformation of family relationships and roles, and the placing of new burdens on both the patient and family caregivers. Altilio and Rigoglioso (108) argued that payers and providers have moral and ethical responsibilities toward caregivers. Such responsibilities range from viewing the caregiver as a member of the health care team and involving them in all aspects of care planning to providing ongoing support, after-care, and bereavement care. Their plan includes the provision of improved insurance coverage for both the ill family member and the caregivers. Altilio and Rigoglioso noted that increased involvement in the care team may help caregivers feel more prepared to manage the huge challenge of home care. Conversely they also mention that there are dangers in incorporating caregivers as members of the treatment team because professionals may feel the right to abdicate their own responsibilities to the overburdened caregiver. Essentially, Altilio and Rigoglioso call for a paradigm shift in viewing caregivers. They assert that health care providers should be major advocates for caregivers in order to improve discharge planning to home care, provide ongoing education, skills training, and support, and simplify insurance coverage policies. This latter point is especially important because it would allow families to know exactly what to expect and how to safeguard against failure for lack of knowledge or understanding.

Assessment of Symptoms

Assessment of both acute and chronic symptoms can be difficult in the home. In the absence of diagnostic facilities and multidisciplinary specialists, care must be taken to avoid attributing symptoms to preexisting illness. Underreporting of symptoms may be common for a variety of reasons. Cancer patients may not report pain because they fear the social implications of opioid analgesics. Elderly patients are often stoic and dread additional diagnostic tests, hospitalization, and new medications (73,74). Although home care nurses and family caregivers may be extremely helpful, most patients require careful evaluation of significant new complaints as well as continued assessment for the management of chronic or persistent symptoms.

Patients with chronic pain should be evaluated for psychological problems. Functional assessment, including ambulation and a broad variety of activities, may represent important indicators of overall physical well-being. Most patients with chronic pain also have significant anxiety or depression at some time. The need to identify and manage anxiety and depression cannot be overemphasized in the adjunctive management of chronic pain, because ongoing symptoms have been shown to significantly affect general emotional well-being, adjustment to illness, cognition, pain perception, and overall treatment outcome (109,110,111 and 112). Formal assessment screening instruments for functional and psychological impairments are helpful in this evaluation and minimize the possibility that detectable problems will be missed (75,113,114,115 and 116).

Nondrug Treatments

In addition to the extensive responsibilities related to the pharmacological management of pain, patients and family caregivers use many nondrug strategies for pain relief at home. The home care environment offers the benefit of access to nondrug pain relief methods, and patients and families often feel more comfortable with these alternative methods at home. Previous research has demonstrated that patients and family caregivers infrequently receive formal information or guidance regarding nondrug strategies but rather rely on their own attempts to discover methods that may add to the patient's comfort (23,45,58).

Since 1991, our program of research at the City of Hope has evaluated a structured program for introducing nondrug pain methods at home. These interventions include both physical and cognitive methods. Physical means of pain relief include such interventions as heat, cold, and massage, and cognitive strategies include relaxation, imagery, and a variety of distraction techniques (117,118). Studies have demonstrated a marked decrease in anxiety and depression, especially at the end of life, when such nonpharmacological techniques are incorporated into traditional treatment regimens (119,120 and 121). Given the increase in attention to complementary therapies, the National Institutes of Health conducted an extensive study evaluating the efficacy of various nontraditional modalities. Their conclusion confirmed the benefits of certain types of complementary medicine on treating cancer pain (122).

Our experience has also demonstrated that patients and families are very eager to add nondrug interventions to their overall pain management (117,118). These provide great benefit to the patient by not only enhancing physical relief but also alleviating anxiety and giving the patient a better sense of control. We have also demonstrated that family caregivers have found nondrug comfort measures to be extremely valuable in reducing their sense of helplessness. Families are very eager to learn skills that will add to the patient's comfort. It is these family interventions that are often recalled during bereavement as positive memories of their ability to provide greater comfort during terminal illness.

Other more structured interventions can also be incorporated by referral to health care professionals such as clinical psychologists, psychiatrists, social workers, and others who can offer many other treatments that might assist in the patient's comfort at home.

EDUCATING CAREGIVERS

Although there is much evidence demonstrating the need for educating caregivers, few programs have been developed to address the intricate components and complex issues related to providing care to chronically or terminally ill in the home.

Cancer Pain Education for Patients and the Public

Beginning in the early 1990s structured pain education interventions were offered by the City of Hope investigators to assist patients and families at home (123). In 1994, the researchers extended such training into communities. The research was divided into two phases. In phase I (1994–96), the intervention was transferred to home care nurses to integrate pain education in their home care visits. Essentially, phase I focused on issues related to the integration of pain education into routine home care services. From 1996 to 1998, phase II focused on the evaluation of effectiveness of intervention implemented by the home care clinicians.

From those initial programs evolved a larger, more comprehensive effort to extend such training nationwide. In this effort to address the needs of caregivers and to improve patient and public education, Ferrell and colleagues at the City of Hope National Medical Center in Duarte, California, developed and implemented educational programs targeted toward staff from hospitals, ambulatory care, hospices, home care settings, and consumer groups. Thus, the Cancer Pain Education for Patients and the Public (CPEPP) program is designed as a “train the trainers” model to educate staff working directly with patients and the public. Following such training participants return to their communities and offer training to patients and the public, essentially caregivers. Although CPEPP is designated for cancer pain patients, its principles can be applied to other disease-specific groups. The general training guidelines of caregiving education can be standardized for preparing lay members of the community. The CPEPP program will offer three national programs of training with follow-up. The long-term evaluation of influencing patients, the public, and family caregivers, will be forthcoming. It is the hope of the investigators that such a model will be the beginning of a trend to meet the training needs of caregivers and the health care professionals with whom they interface.

In other studies Ferrell and colleagues recognized the limitations and challenges that health care professionals face in attempting to train patients and their caregivers (124). They asserted that the health care field must explore innovative methods of training, such as trained volunteers or peer educators, while overcoming significant

barriers of time and limited resources to achieve such goals. Key to any strategy developed will be the incorporation of the principles of effective teaching and learning.

Other Efforts of Preparing Family Caregivers

In a review of literature from 1975 to 1999, Pasacreta and McCorkle (86) found a dearth of data-based literature and limited number of well-designed training programs for caregivers. The limited programs that were discovered represented three broad categories: (a) educational, (b) counseling/psychotherapeutic, and (c) hospice/palliative home care. Of those dimensions of training, most interventions were aimed at individuals or families, typically were located at one facility, and often represented selection bias in well-adjusted caregivers. Nonetheless the disparate and limited attempts at training caregivers further highlights the extent of the need. Pasacreta and colleagues discovered that a 6-hour psychoeducation program for cancer caregivers had a positive influence on several factors (85,86). For instance, caregivers relayed an improved sense of confidence in providing care as well as improved perception of their own health. The focus on skills and application of principles was particularly noteworthy as the training addressed symptom management, psychosocial support, and resource identification.

In an effort to increase communication and collaboration between health care professionals and family caregivers, the Children's Hospital in Philadelphia, Pennsylvania, developed a unique training program that placed family members as faculty (125). The “Family Faculty” trains parents of children with special health needs to present classes on family-centered care to physicians, nurses, and other hospital staff. The underpinnings of the Family Faculty program is based on the philosophy of family-centered care and the belief that health care professionals will learn firsthand the hardships and challenges encountered by family caregivers. Such increase in insight is expected to enhance understanding that would lead to better treatment planning and coordination between providers and families.

Resources for Caregivers

Since the middle 1990s, researchers and clinicians have recognized the need to develop resources specifically aimed at family caregivers. Stetz, McDonald, and Compton (126) discovered five major categories of informational needs of family caregivers: (a) preparing the caregiver, (b) managing the care, (c) facing challenges, (d) developing supportive strategies, and (e) discovering unanticipated rewards and benefits. These researchers asserted that health care professionals have a responsibility to prepare family members with educational strategies that include skill development, access to and use of resources, home care management, decision-making, and self-care.

Levine (38) has highlighted projects that were developed in the 1990s to create “step-by-step” guides on home care principles for lay caregivers. For instance, the Visiting Nurses Association (127) published the *Caregiver's Hand-book: A Complete Guide to Home Health Care* as a reference tool for lay family members as well as to assist new professionals in the field. Other such guides are available for caregivers including a fully illustrated book entitled *The Comfort of Home: An Illustrated Step-by-Step Guide for Care-givers* (128). Many other such resources have become available for family members who find themselves in the throes of having to manage the home care of their loved one. While such informational materials can be enormously helpful, the caregiver is met with the challenge of finding sufficient time to study the techniques and principles they offer.

Within the context of caregiver preparation, it is important to highlight nongovernmental, nonprofit organizations that have burgeoned in the latter part of the twentieth century. For instance, the American Cancer Society has an extensive network of resources and highly defined materials for caregivers as well as for patients. The Wellness Community also serves an important function in providing group support for patients and their families. Cancer Care, a New York-based group, is another organization established exclusively to develop and offer resources to patients and caregivers. Yet these organizations do not offer practical training in caregiving skills.

Just as the technology boom has advanced medical treatments, it has also allowed greater access to resources for caregivers. If a family is fortunate enough to own a computer and have access to the Internet, a wealth of information is available. Moreover, many treatment centers have created “information centers” that allow access to the World Wide Web. Although such an environment can offer volumes of material, caregivers will have to be cautious not to become further inundated and to find the time and energy to pursue such resources. The fact that such items are available within moments represents a step forward in trying to prepare caregivers for their “other full-time job” of managing the home treatment of their loved ones.

Public Policy Implications

To examine trends in end-of-life care across generations, Byock initiated a 10-year longitudinal study in Missoula, Montana (15). That project seemed to bring national attention to end-of-life care, and it seemed to propel new efforts in advocacy and public policy in that field. Despite the increase in advocacy efforts to enhance federal allocation of funding for home care efforts and the needs of caregivers, little has been done at the federal level to lessen the burden. At the outset of the twenty-first century, home care continues to face enormous and increasing challenges with decreased funding. The burden on health care professionals as well as on families has increased exponentially in the past decade. With the expanding aging populations, home care will likely take on a different look in the new millennium (21,129).

In the late 1990s several U.S. senators attempted to pass legislation that would increase resources and rights for endof-life care, including aspects of home care. Such legislation never passed Congress. As a result efforts increased to pursue federal legislation that would include special benefits for caregivers. In early 2001, a new program was launched that offers $113 million in grants to states under a new National Family Caregiver Support Program. In November 2000 Congress created the new caregiver program as part of the Older Americans Act Amendments. The central element of the program consists of grants to states distributed through a congressionally mandated formula. Other components include innovative, competitive grants and a new Native American Caregiver support program. Ideally the funds allocated will allow programs at the state level to provide critical support, such as home and community-based services, including information, assistance, training, counseling, support, and respite opportunities for caregivers. Essentially the programs are aimed at allowing families to maintain their caregiver roles.

This is particularly relevant when considering the cost of caregiving. In 1997, the national economic value of informal caregiving—care provided by an untrained family member—was $196 billion, dwarfing the national expenditures of $32 billion for formal home health care and $83 billion for nursing home care. Notably the estimated economic value of informal caregiving represents approximately 18% of the total national health care expenditures (38). Although the outcome of the new $113 million caregiver program remains to be seen, at least there seems to be some recognition of the value and important role of family caregivers as well as the tremendous toll that providing such care takes on an individual and whole family systems.

In addition to governmental factors, other policy experts have attempted to influence whole systems of care. In the late 1990s, Lynn, founder of the Center to Improve Care of the Dying as well as the advocacy group, ABCD, proposed a comprehensive system of managed care of endof-life care. Her program, Medicaring, is based on the notion that capitated or salaried managed care systems offer important opportunities to provide high-quality, costeffective care for seriously ill individuals nearing the end of life (130,131). Despite the fact that managed care systems for the most part have largely ignored the need for end-of-life care, Lynn argues that such systems inherently offer certain advantages that include coordinated care across delivery systems, interdisciplinary teams, integrated services, service arrays, utilization controls, and accountability for care standards. Capitated or salaried managed care systems may be well positioned to achieve marked change in end of life if they were to broaden their current focus to include end-of-life care and if payment reimbursements were revised to encourage such programming. The focus of managed care systems on prevention, patient education, cost efficiency, service coordination, integrated provider networks, and such organizational structures could potentially support real change in end-of-life care. Indeed some managed care organizations have expanded services to hospices, albeit with extensive limits. Lynn asserts that her “Medicaring” proposal encompasses the best components of palliative care within a structured managed care system. Such a program would be comprehensive and supportive and would offer community-based services to meet personal and medical needs with a focus on patient preferences, symptom management, family counseling, and support (131). Home care would be profoundly influenced if such a program became the standard of care in community-based managed care organizations. It is a larger system and societal change that needs to occur before such programs are institutionalized.

ENHANCING PROFESSIONAL TRAINING IN HOME CARE

Home Care Outreach for Palliative Care Education

Although palliative care principles are prevalent in hospice programs, such elements have not necessarily extended into other health care systems such as home care. This dearth of training exists despite the fact that home care agencies provide extensive care to patients and families facing physical and psychosocial demands at the end of life. Even though nonhospice home care agencies are technically not intended for terminally ill, palliative care education is important to support home care providers given the challenges of the health care system in general and the greater demands on home care, essentially making it the primary setting of care (132).

Beginning in the middle 1990s, Ferrell and colleagues developed and implemented the Home Care Outreach for Palliative Care (HOPE) project to: (a) assess current practices within select nonhospice home care agencies regarding care of the dying, (b) design the HOPE educational program to include relevant content for realistic implementation in home care agencies, (c) implement the HOPE project in select home care agencies, and (d) assess outcomes of the project and plan for future dissemination to home care agencies and organizations.

The HOPE curriculum is organized into five modules. The first module presents a general overview of palliative care and end-of-life issues. The second and third modules address various aspects of pain and symptom management, respectively. The fourth component focuses on communication, family caregivers, and

spirituality. The last module, entitled “the good death,” covers important elements of the last days of life. Key aspects of the modules are the attention given to psychosocial dimensions of care at home, cultural considerations, and the special care required at the time of death. In early 2001, the HOPE project was extended to a national training group with planned followup studies and additional programs scheduled. The first of its kind in a “train the trainers” format for palliative care education of home care providers, the HOPE project is aimed at changing the landscape of end-of-life care in the home care setting (4,132,133).

Communication Training

Of interest, the retrospective assessment provided by caregivers after the death of their family member is in large part influenced by how they viewed the relationship and communication with the health care professional (134). Missing components of “model” treatment programs can be overlooked if the caregiver feels sufficiently supported by the health care community (135). However in palliative care and home care studies, patients and their families are often dissatisfied with their interactions with health professionals (136). That may come as no surprise when one considers that ironically medical professionals spend up to 70% of their working time communicating but have virtually no education in that aspect of their work (134). Yet communication behaviors seem to play an important role in meeting the cognitive and affective needs of patients with cancer as well as the needs of their caregivers (137). Moreover, communication skills are particularly imperative in home care settings with its myriad of family dynamics, along with cultural, ethnic, and religious nuances of the home. Such issues have prompted researchers to develop training in communication skills for health care professionals (137,138). Adding another component of training to an already overburdened health care professional may not be a welcome endeavor. However some studies have demonstrated that such training has actually helped to reduce the intensity of the emotionally laden interactions and increase the professional's sense of confidence to adequately address the affective components of life-threatening illness and care (136,137).

Cultural Competency

Health care providers must be prepared to manage diverse, multicultural patient populations in various health care settings while working collaboratively with coworkers who also represent various cultural backgrounds (90). Home care presents a greater challenge in that the health care provider is essentially being immersed into the microculture of the family and the macrocosm of the community. Health care educators have recognized this changing demography of our culture, and some have developed programs in cultural competency for their workers (90). Of note, cultural competency does not necessitate that health care providers know and understand all the traditions and practices of the numerous ethnic groups. Rather the intent is to have managers, administrators, and front-line employees work collectively to increase their knowledge of cultural diversity, share that knowledge, and combine efforts to promote cultural awareness and sensitivity in practice settings (90).

Patient education efforts also have developed in the past few decades (96), and researchers advocate that health care professionals must consistently exercise heightened cultural sensitivity through their approach to patients as well as in information provided (90,139). Failing to do so runs the risk of necessitating more time and resources (93).

Davis (140) asserts that health care professionals traditionally have established a portrait of the “ideal dying patient,” which implicitly places expectations on terminally ill patients with whom they come in contact. Such tacit anticipation runs the risk of causing a chasm between the health care provider and the patient and family. This may further heighten emotionally laden situations and make care and treatment even more complicated. In addition, lack of recognition of cultural factors may cause further difficulties in communication and understanding with regard to informed consent and truth-telling about diagnosis, prognosis, and treatment options (141).

As a result of the potential dangers associated with lack of recognition and training in multicultural care, Lister (142) presented a taxonomy for developing cultural competence among health care providers. Of interest, some policy advocates have argued for licensing boards to require cultural competency as a provision of licensure. Rather than adding more demands to the taxed home care system, De Savorgnani and Haring (143) assert that the impact of cultural issues on home care has the potential to serve as the impetus for development of “comprehensive diversity programs” that would enhance the lives of patients and staff in home care. Consistently in the past decade, researchers have demonstrated the benefits of a culturally sensitive staff as patients and their families have reported that they view their homes as the milieu that allows for continuity of lifestyle, family relationships, and cultural values (144,145). Many professional organizations now view transcultural training as a necessity given the changing demographics in the United States and in home care.

CONCLUSION

The home care environment can best be described as the intensive care unit of the future. Home care is complex as a result of changing patient and family caregiver characteristics. The home environment is rich with benefits to enhance patient comfort, but it also provides challenges in providing optimum physical, psychosocial, and spiritual care. The literature has addressed many interventions that are helpful in assisting families in home care (Table 56-2). These interventions include a range of suggestions about physical care, including the transferring of information about physical caregiving back to families, offering validation and support to families for their efforts at home care, and interventions to improve communication.

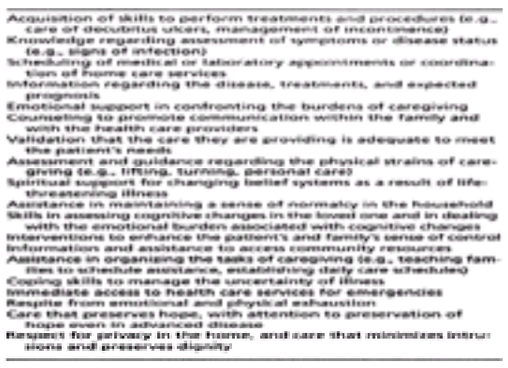
Acquisition of skills to perform treatments and procedures (e.g., care of decubitus ulcers, management of incontinence)
Knowledge regarding assessment of symptoms or disease status (e.g., signs of infection)
Scheduling of medical or laboratory appointments or coordination of home care services
Information regarding the disease, treatments, and expected prognosis
Emotional support in confronting the burdens of caregiving
Counseling to promote communication within the family and with the health care providers
Validation that the care they are providing is adequate to meet the patient's needs
Assessment and guidance regarding the physical strains of caregiving (e.g., lifting, turning, personal care)
Spiritual support for changing belief systems as a result of life-threatening illness
Assistance in maintaining a sense of normalcy in the household
Skills in assessing cognitive changes in the loved one and in dealing with the emotional burden associated with cognitive changes
Interventions to enhance the patient's and family's sense of control
Information and assistance to access community resources
Assitance in organizing the tasks of caregiving (e.g., teaching families to schedule assistance, establishing daily care schedules)
Coping skills to manage the uncertainty of illness
Immediate access to health care services for emergencies
Respite from emotional and physical exhaustion
Care that preserves hope, with attention to preservation of hope even in advanced disease
Respect for privacy in the home, and care that minimizes intrusions and preserves dignity

TABLE 56-2. INTERVENTIONS FOR ASSISTING FAMILIES IN HOME CARE

There is a tremendous need for continuity of care as patients are increasingly cared for across many settings. It is essential that issues of care in the home are communicated to those involved in ambulatory care, inpatient care, and other areas of care. Expert care for patients at home, similar to all aspects of palliative care, begins with a thorough assessment of the patient's needs. Organized care based on a comprehensive perspective, which recognizes the physical, psychological, social, and spiritual needs during advanced illness, is best accomplished by empowering families to provide excellent care for patients at home.

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MANAGEMENT OF SYMPTOMS IN THE ACTIVELY DYING PATIENT

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The obligation of physicians to relieve suffering is universal, particularly when death is imminent and the indignities of illness consume patients' final days and hours of life. This honored encumbrance transcends all other duties accorded physicians and is fundamental to a death free of interminable symptoms and a satisfactory bereavement for surviving family members (1). Lamentably, the dying process can be a time of untold loss and suffering, and although spiritual and psychosocial concerns are basic domains in the inherent makeup of an individual, unrelieved physical suffering can detract from attention to important spiritual and psychosocial issues at the end of life. Accordingly, physicians must be competent in relieving physical distress and in so doing maintaining patient dignity and familial equanimity (2).

During the last days of life, there are characteristic symptoms that commonly occur, including dyspnea and noisy, gurgling respirations frequently referred to as the “death rattle,” anxiety, restlessness, delirium, nausea and vomiting (NV), and pain (2,3,4,5,6,7,8 and 9). Although such symptoms are often multifactorial in etiology, treatment is usually empiric and palliative. Diagnostic evaluation is limited in recognition of the short life expectancy and impending death. Nevertheless empiric treatment strategies do not suggest or encourage clinical indifference but rather mandate ongoing clinical assessment of therapeutic interventions in a continual effort to allay suffering. From time to time terminal symptoms are refractory and unresponsive to aggressive and exhaustive interventions. In such cases palliative sedation (PS) is an ethically and morally appropriate option that may be utilized to afford a more peaceful and tranquil death and a satisfactory grieving process for remaining family members.

DYSPNEA AND THE DEATH RATTLE

Dyspnea

Dyspnea occurs in 29–90% of terminally ill patients and is frequently the most common severe symptom as death approaches (9,10,11,12 and 13). Although it is more common in patients with pulmonary disorders, 23.9% of dyspneic patients in the National Hospice Study did not exhibit cardiac or pulmonary disease (11). Dyspnea in terminally ill patients derives from five primary causes: (a) existing disease [i.e., chronic obstructive pulmonary disease (COPD) and congestive heart failure], (b) acute superimposed illness (i.e., pneumonia, pulmonary embolus), (c) cancer-related complications (i.e., pleural effusion, lymphangitis carcino-matosis, tumor-induced bronchial obstruction, ascites), (d) effects of cancer therapy (i.e., radiation and chemotherapy-induced pulmonary fibrosis), and (e) miscellaneous causes (i.e., anemia, uremia, anxiety) (9,13,14).

As with any symptom, the treatment of dyspnea should address any easily correctable underlying cause, all the while recognizing and considering the limited life expectancy of the imminently dying patient and the invasiveness and discomfort of proposed therapeutic interventions. Consequently for most patients near death, opioids, benzo-diazepines, phenothiazines, and corticosteroids are the mainstays of therapy (2,7,8 and 9,12,13,14 and 15).

Opioids purportedly relieve dyspnea by altering the perception of breathlessness (10,16), decreasing ventilatory response to hypoxia and hypercapnia (10,17), and reducing oxygen consumption at rest and with exercise (10,18). Controlled trials and anecdotal case reports on the use of systemic opioids in the treatment of malignant and COPD-associated dyspnea have generally demonstrated a reduction in dyspnea, with many patients in the various studies already receiving opioids for pain control (10,15,19,20,21,22 and 2323). Although morphine preparations are generally utilized, any opioid potentially should alleviate dyspnea (Table 57-1). Opioids can be administered orally, rectally, sublingually, subcutaneously, intravenously, and by inhalation, but during the final hours of life when the ability to swallow declines and consciousness wanes, rectal, subcutaneous, and intravenous routes are more commonly used.

TABLE 57-1. PHARMACOLOGICAL TREATMENT OF TERMINAL DYSPNEA

Inhalation of opioids is a unique and innovative approach to drug delivery. Controlled trials have revealed conflicting results (15,19,23,24,25,26 and 27), but anecdotal reports have generally been favorable (13,28,29 and 30). It is postulated that inhaled opioids exert their effect by means of opioid receptors that have been identified in the bronchial mucosa, as pharmacokinetic studies suggest that systemic bioavailability of nebulized morphine is extremely poor, varying from 4% to 8% (19,27,31). However, opioids also may stimulate histamine release from pulmonary mast cells and precipitate bronchospasm, worsening terminal dyspnea. Because this complication is usually a first-dose effect, careful observation should occur during initial administration. Contrary to many clinicians' belief that the use of preservative-free opioid preparations prevents histamine release, bronchospasm may still occur (27). Although studies are contradictory and further research is unquestionably warranted, in the dyspneic patient near death, nebulized opioids may be efficacious and worth a trial in an attempt to reduce breathlessness and assuage the horrific fear of suffocation.

Benzodiazepines have been frequently utilized in dyspnea primarily when a component of anxiety is involved. Studies and anecdotal reports are contradictory (15), with no well-designed controlled trials evident in cancer patients (24). Nevertheless benzodiazepines are frequently beneficial in reducing dyspnea, particularly during the final days of life (32) and are increasingly used in hospice and palliative care programs. Buspirone, a popular nonbenzodiazepine anxiolytic and serotonin agonist, has been shown to relieve dyspnea in patients with anxiety and COPD at a dose of 15 mg to 45 mg daily (33). Because of its delayed onset of action, it may be of limited use in actively dying patients. Although not a benzodiazepine, the neuroleptic chlorpromazine has been used in dyspnea refractory to other medications. It appears to reduce air hunger and anxiety with minimal side effects (primarily sedation and hypotension) and has been efficacious in patients near death (9,34,35).

Although corticosteroids are useful when bronchospasm is associated with inflammation, most studies suggest that only 20% to 30% of patients with COPD improve with corticosteroid therapy. In the final days of life corticosteroids are most useful when prescribed for dyspnea associated with airway obstruction, lymphangitis carcinomatosis, radiation pneumonitis, and superior vena cava syndrome (9,14). Corticosteroids can be administered orally, rectally, subcutaneously, intravenously, and by inhalation. Although side effects are of concern during chronic use, such concerns are negated by short-term use in dying patients.

Other medications also are available to attenuate dyspnea in the dying patient. These include diuretics, bronchodilators, and inhaled anesthetics. Diuretics are useful when pulmonary edema and ascites contribute to dyspnea. Although bronchodilators are best utilized in patients with a bronchospastic component to dyspnea (i.e., asthma, COPD with reactive airways), these drugs frequently are used when there is little-to-no evidence of bronchospasm and appear to provide subjective reduction of dyspnea in many patients. The use of adrenergic agonist bronchodilators, such as albuterol and metaproterenol, should be tempered by the possibility of resultant agitation, tremor, and heightened anxiety, potentially aggravating terminal dyspnea (9).

Nebulized anesthetics have been used infrequently for dyspnea in dying patients. In a study comparing nebulized saline and lidocaine, saline exerted a greater effect on the reduction of breathlessness (27,36). However nebulized anesthetics have been useful for cough and may be considered when persistent coughing contributes to or aggravates dyspnea (27).

Nonpharmacological interventions that are useful for terminal dyspnea include oxygen, a bedside fan, thoracentesis for pleural effusion, and paracentesis for ascites. The role of oxygen therapy in reducing dyspnea in patients near the end of life is somewhat controversial. In hypoxemic patients with disorders such as COPD, congestive heart failure, or pulmonary fibrosis, most studies suggest that there is significant symptomatic improvement (19,24,37). In patients without hypoxemia, however, its use is more contentious. Even so, oxygen therapy may alleviate dyspnea by way of a placebo effect and should be considered in actively dying patients (a nasal cannula is better tolerated than a mask) (9). Moreover oxygen therapy may provide many family members with the symbolic solace that “something is being done” to help their loved one in spite of the fact that oxygen may actually provide little therapeutic benefit.

A bedside fan may also be useful in alleviating dyspnea by reportedly stimulating thermal and mechanical receptors of the trigeminal nerve in the cheek and nasopharynx, altering the perception of breathlessness (9,38,39). The fan should be placed at the bedside, set on a low speed, and directed at the patient's face (9).

Thoracentesis and paracentesis may be useful when pleural effusion and ascites contribute to dyspnea (particularly if previous drainage has reduced dyspnea). In the final days of life, however, other strategies generally should be utilized unless noninterventional approaches have failed and breathlessness aggravates suffering.

Death Rattle

In the last 24–48 hours of life, most patients retain secretions in the back of the throat that produces a gurgling type of respiration frequently referred to as the death rattle (9,40). Fortunately, the patient is usually unaware of the noise. It can, however, be very disturbing to family members. Oropharyngeal suctioning is usually provided, but gagging and coughing may generate patient discomfort and further distress for relatives and caregivers. Instead, treatment with anticholinergic drugs is recommended to desiccate bronchial secretions and abolish the need for suctioning. Suggested medications include atropine, glycopyrrolate, scopolamine, and hyoscyamine (Table 57-2) (9,14). These antisialagogues do not dry up secretions already present, and they should therefore be used at the first sign of noisy respirations (7). In addition, placing patients in a lateral recumbent position with the head slightly elevated may help reduce the pooling of secretions and diminish noisy respirations (2).

Drug	Dose
Scopolamine	0.4–0.6 mg s.q. q2–4h; 0.8–2.0 mg CSI q24h; 1–3 transdermal patches q3d
Hyoscyamine	0.125–0.250 mg s.l. q2–4h; 0.25–0.5 mg s.q. q2–4h; 1–2 mg CSI q24h
Glycopyrrolate	0.2 mg s.l., s.q. q2–4h
Atropine	0.4 mg s.q. q2–4h; may give 2 mg of atropine, 2.5–5.0 mg of morphine, and 2 mg of dexamethasone q2–4h via nebulizer

CSI, continuous subcutaneous infusion.

TABLE 57-2. PHARMACOLOGICAL TREATMENT OF THE DEATH RATTLE

ANXIETY, RESTLESSNESS, AND DELIRIUM

Anxiety

Anxiety is one of the most common psychological problems in terminally ill patients and like many symptoms can have numerous etiologies (41,42,43,44 and 45). Anxiety can be a component of a preexisting anxiety disorder or, more commonly in actively dying patients, accompany medical disorders and complications of illness and medications (42,44). Medical disorders that can cause anxiety include hyperthyroidism, pheochromocytoma, and primary and metastatic brain tumors. Medical complications and medications that can precipitate anxiety include hypoxia, sepsis, unrelieved pain, dyspnea, and medications such as corticosteroids, bronchodilators, and antiemetics that cause akathisia (41,42,43 and 44). In addition, withdrawal states from benzodiazepines and opioids can result in anxiety and may occur inadvertently when medications are suddenly discontinued after admission to a hospital or long-term care facility (43).

The treatment of anxiety in the terminally ill often depends on etiology but generally involves nondrug maneuvers, specific interventions, and pharmacotherapy. Nondrug measures include meditation, biofeedback, progressive relaxation, and psychotherapy (43). In actively dying patients these nondrug methods are of little value. In some cases specific interventions can be of benefit and include such measures as oxygen and opioids for dyspnea, opioids and other analgesics for pain, and discontinuing medications that cause akathisia.

The principal therapy for anxiety includes the judicious use of benzodiazepines, neuroleptics, and antihistamines (41,42,43 and 44). Benzodiazepines are the mainstay of treatment in the terminally ill patient, with the shorter-acting agents, such as lorazepam and oxazepam, preferred in the patient with advanced disease (Table 57-3). These drugs are metabolized by conjugation in the liver and are safest when hepatic disease is present (41,42,44). This is in contrast to alprazolam and other benzodiazepines which are metabolized through oxidative pathways and may accumulate in debilitated patients (46). Midazolam, a water-soluble benzodiazepine, may be infused intravenously or subcutaneously and is very useful in controlling anxiety in the terminal phase of illness. The cost of midazolam may limit its use (41,42,43 and 44,47), particularly in managed care and capitated health systems. Diazepam, an older but efficacious benzodiazepine, may be used rectally when no other route is available and cost is of concern, with recommended dosages equivalent to oral regimens. Clonazepam, a longacting benzodiazepine used for seizure disorders and myoclonus, is useful in patients who experience end-of-dose recurrence of anxiety on shorter-acting benzodiazepine medications (41,42,43 and 44).

Drug	Dose[a]
Benzodiazepines	
Lorazepam	0.5–2.0 mg p.o., s.l., i.m., i.v., s.q. q1–4h
Midazolam	0.5–5.0 mg i.v., s.q. q1–4h; 10–30 mg CSI q24h
Diazepam	2.5–10.0 mg p.o., i.m., i.v., p.r. q1–4h
Clonazepam	0.5–2.0 mg p.o. b.i.d.–q.i.d.
Oxazepam	15 mg p.o. t.i.d.–q.i.d.
Neuroleptics	
Haloperidol	0.5–1.0 mg p.o., i.m., i.v., s.c. q1–6h
Chlorpromazine	10–25 mg p.o., i.m., i.v., p.r. q4–6h
Thioridazine	10–75 mg p.o. t.i.d.–q.i.d.
Antihistamines	
Hydroxyzine	10–50 mg p.o., i.m., i.v., s.q. q2–4h

CSI, continuous subcutaneous infusion.
[a]Suggested starting doses, may need to be clinically titrated; older frail patients may need doses adjusted appropriately, may be difficult for actively dying patients to take oral medications.

TABLE 57-3. PHARMACOLOGICAL TREATMENT OF ANXIETY

Other nonbenzodiazepine medications useful for anxiety include the neuroleptics chlorpromazine, thioridazine, and haloperidol, and the antihistamine hydroxyzine

(Table 57-3). Neuroleptics may be used when benzodiazepines fail to relieve anxiety, when psychotic symptoms accompany anxiety, or when there is concern regarding the respiratory depressant effects of benzodiazepines (48). Hydroxyzine, an effective antihistaminic anxiolytic, may have coanalgesic effects (49) and may be a particularly useful alternative to benzodiazepines when pain accompanies or exacerbates anxiety, or when benzodiazepines and neuroleptics are contraindicated (i.e., allergy, respiratory depression, akathisia).

Restlessness

Restlessness is commonly observed during the last hours of life. Although it has multiple causes (and may overlap with delirium), specific treatment may not be possible (7). Restless patients may have diverse symptoms, including impaired consciousness, intermittent sleepiness, tossing and turning, moaning, grunting, crying out, and agitation and muscle spasms or twitching (2). Restlessness may be caused by spiritual conflicts, physical discomfort, such as a distended urinary bladder or bladder spasms, fecal impaction, unrelieved pain, and pressure ulcers, or by nausea, dyspnea, pruritus, hypoxia, extreme weakness, corticosteroids, and sudden withdrawal from benzodiazepines. Treatment involves identifying and managing the underlying cause or, if that is not possible, providing spiritual support, verbal and tactile reassurance, and utilizing a benzodiazepine, such as midazolam, or a neuroleptic, such as chlorpromazine (Table 57-3) (2,7).

Delirium

Delirium is a nonspecific global disorder of cognition and attention that occurs in 8% to 75% of hospitalized cancer patients (43,44,50,51) and in 62% of patients just prior to death (52,53). It is a significant sign of physiological disturbance and, analogous to anxiety, may be secondary to multiple etiologies, including primary or metastatic brain tumors, infection, organ failure, metabolic disturbances, vascular complications, nutritional deficiencies, medication side effects, and a paraneoplastic syndrome (52). In contrast to dementia, delirium is considered a reversible disorder with rapid onset; in the last 24 to 48 hours of life, however, it may be irreversible. According to the Diagnostic and Statistical Manual of the American Psychiatric Association (54), delirium is characterized by

- Disturbance of consciousness (reduced awareness of the environment) with reduced ability to focus, sustain, or shift attention,
- Change in cognition (memory deficit, disorientation, perceptual disturbances such as hallucinations, illusions, delusions) that is not related to a preexisting dementia,
- Development over a short period of time, with usual fluctuation throughout the day, and
- Evidence from the history, physical examination, or laboratory tests of a general medical condition judged to be etiologically related to the causation of delirium.

The assessment of delirium must take into consideration the life expectancy of the patient and the patient's goals for care. Most palliative care clinicians would undertake a diagnostic workup only when a clinically suspected cause can be easily identified and treated effectively with simple interventions that carry a minimal burden or risk of causing further distress (i.e., hypodermoclysis for dehydration). Most often, the cause of delirium in the actively dying patient is multifactorial and irreversible, and treatment is usually empiric (52). Similar to anxiety, nondrug supportive measures are of limited value (other than the presence of family members, a well-lit room, and familiar sounds and music). Consequently pharmacological interventions are the primary methods for treating delirium in patients near death.

Neuroleptic medications are the preferred pharmacological agents and are particularly safe and efficacious in reducing disturbing cognitive symptoms in dying patients (Table 57-4) (14,41,42,43 and 44,50,52). Haloperidol is the usual drug of choice and may be given orally, intravenously, and subcutaneously. However clinicians should be aware that parenteral doses are approximately twice as potent as oral doses (50,52). It is the drug of choice because of its short half-life, lack of active metabolites, and minimal anticholingeric and cardiovascular side effects. It is also less likely to cause sedation or paradoxical delirium (55). Unfortunately, extrapyramidal symptoms and movement disorders may occur with the use of haloperidol and other neuroleptics and require the use of antiparkinsonian drugs, such as diphenhydramine, benztropine, and trihexyphenidyl, and beta blockers, such as propranolol, for akathisic movements.

Drug	Dose[a]
Neuroleptics	
Haloperidol	0.5–1.0 mg p.o., i.m., i.v., s.c. q1–6h; 5–15 mg CSI q24h; in acute situations, 0.5–1.0 mg i.v., s.q. q45–60 min until symptoms controlled
Chlorpromazine	10–25 mg p.o., i.m., i.v., p.r. q4–6h
Risperidone	0.5–1.0 mg p.o. b.i.d.
Benzodiazepines	
Lorazepam	0.5–2.0 mg p.o., s.l., i.m., i.v., s.q. q1–4h
Midazolam	0.5–5.0 mg i.v., s.q. q1–4h; 10–30 mg CSI q24h

CSI, continuous subcutaneous infusion.
[a]Suggested starting doses, may need to be clinically titrated; older frail patients may need doses adjusted appropriately; may be difficult for actively dying patients to take oral medications if the patient is taking an opioid; rotating to another opioid with no active metabolites (i.e., hydromorphone) may help lessen delirium if the delirium is opioid-induced; severe agitated delirium may require palliative sedation.

TABLE 57-4. PHARMACOLOGICAL TREATMENT OF DELIRIUM

A short-acting benzodiazepine can be added if the patient is overly agitated, even though benzodiazepines alone are not indicated in the treatment of delirium. In fact, benzodiazepines may actually exacerbate the delirious state and should be used cautiously and discontinued if delirium worsens. When delirium is difficult to control in the last days of life, PS to the point of unconsciousness may be needed (6,56). In such situations a benzodiazepine, such as lorazepam or midazolam, is the drug of choice, either alone or in conjunction with a neuroleptic.

NAUSEA AND VOMITING

Nausea and vomiting occur in 62% of terminal cancer patients. Although the prevalence is 40–46% during the last 6 weeks of life (57), it rarely develops as a new symptom during the last days of life (8). NV is observed more frequently in women, persons younger than 65 years of age, and patients with stomach and breast cancer (57).

The etiology of NV in terminal illness varies and is frequently multifactorial (9), particularly as death approaches. Although diagnostic evaluation can be done, in the actively dying patient, treatment usually involves the empirical use of nonpharmacological measures and antiemetics. However, if the clinician, patient, or family insists on an evaluation, simple tests, such as measurement of electrolytes, blood urea nitrogen, creatinine, calcium, albumin, glucose, and digoxin or anticonvulsant drug levels, are recommended and may readily disclose a reversible cause.

Nonpharmacological measures used to treat NV include dietary manipulations (Table 57-5), elimination of emetogenic medications [i.e., nonsteroidal anti-inflammatories, digoxin, iron (59)], and the limited use of nasogastric suctioning, particularly for high gastrointestinal bowel obstruction. Nasogastric tubes can be uncomfortable and difficult to place, especially in the home environment, but intermittent use may be considered for severe and intractable vomiting refractory to antiemetic therapy. A percutaneous venting gastrostomy is useful if placed prior to the active dying process. However its placement in the patient near death is usually not practical.

Minimize unpleasant odors
Sounds and smells of food preparation should be excluded
Avoid foods known to precipitate nausea and vomiting
Clear liquid diet may be best tolerated
Cold foods may be preferred
Sour foods, such as lemons, and rinsing of the mouth with weak lemon juice may reduce nausea
Utilize frequent small feedings if the patient wants to eat

Adapted from Lichter I. Nausea and vomiting in patients with cancer. *Hematol Oncol Clin North Am* 1996;10:207–220, with permission.

TABLE 57-5. DIETARY MANIPULATIONS FOR NAUSEA AND VOMITING

Nine types of antiemetics are utilized in the treatment of terminal NV: dopamine antagonists, metoclopramide, anticholinergics, antihistamines, corticosteroids, serotonin antagonists, octreotide, cannabinoids, and benzodiazepines (Table 57-6) (9,59,60 and 61). Dopamine antagonists include haloperidol and prochlorperazine and are the usual firstline antiemetics chosen by most clinicians. Haloperidol is an excellent antiemetic and is particularly useful for delirious patients with NV because both symptoms may be improved with a single medication. As mentioned earlier (see the section Delirium), parenteral doses are twice as potent as oral doses, and there is a reported ceiling effect at approximately 30 mg a day. Prochlorperazine is also efficacious and a favorite of many clinicians, and while promethazine and chlorpromazine are also prescribed, there is probably little advantage to using them over prochlorperazine (59). Although combination therapy for NV is common in the terminally ill, two or more dopamine antagonists should not be prescribed concurrently as the potential for adverse extrapyramidal reactions is increased without additional antiemetic benefit.

Drug	Dose[a]
Dopamine antagonists	
Haloperidol	0.5–2.5 mg p.o., i.m., i.v., s.q. q4–6h; 5–15 mg CSI q24h
Prochlorperazine	5–20 mg p.o., i.m., i.v. q4–6h; 25 mg p.r. q8h
Droperidol	2.5–5.0 mg i.v. q4–6h
Promazine	25 mg p.o., p.r. q4–6h; 12.5–25.0 mg i.v. q4–6h
Substituted benzamide	
Metoclopramide[b]	5–20 mg p.o., i.m., i.v., s.q. q6h; 20–40 mg CSI q24h
Anticholinergics	
Scopolamine	0.3–0.8 mg p.o., s.q. q4–6h; 1–2 transdermal patches q3d, 0.4–2.0 mg CSI q24h
Hyoscyamine	0.125–0.250 mg p.o., s.l. q4h; 0.25–0.50 mg s.q. q4–6h; 1.2 mg CSI q24h
Antihistamines	
Buclizine	50 mg p.o. q4–6h
Meclizine	25–50 mg p.o. q4–6h
Diphenhydramine	25–50 mg p.o., i.m., i.v. q4–6h
Corticosteroids	
Dexamethasone	1–4 mg p.o., i.v., s.q. q6h; 2–12 mg CSI q24h
Serotonin antagonists	
Ondansetron	8 mg p.o., i.v., s.q. q8h; 8–24 mg CSI q24h
Granisetron	0.5–1.0 mg p.o., i.v., s.q. q12h
Somatostatin analogue	
Octreotide	150 µg s.q. t.i.d.; 0.2–0.9 µg CSI q24h
Cannabinoid	
Dronabinol	2.5–7.5 mg p.o. b.i.d.–t.i.d.
Benzodiazepines	
Lorazepam	0.5–2.0 mg p.o., s.l., i.m., i.v., s.q. q4h
Compounded medication[c]	
ABHR, ABHRD, ABHRDC	1 p.r. q4–6h

[a] Available as a topical patch, to convert from an oral opioid, convert the opioid to a morphine equivalent dose, then divide the morphine dose by 2 to get the approximate strength of the fentanyl patch. From Storey P, Knight EP, UNMC Hice. assessment and treatment of pain in the terminally ill. Asheville, FL: American Academy of Hospice and Palliative Medicine, 1996, with permission.
[b] Also available as a suppository; hydromorphone also available as a suppository.
[c] Morphine can be compounded into a gel for topical use, bioavailability is unknown.
[d] 1–3 mg/kg bolus; 100 mg/l i.v. over 20–30 min or s.q. over 30–60 min. If pain relieved, start an infusion either i.v. or s.q. at 0.5–2 mg/kg/h; serum levels may be monitored. See Ferrini R. Parenteral ketorolac for severe intractable pain in six hospice patients controlled at home. J Pain Symptom Manage 2000; 19:174–182.
[e] Can be administered by a continuous subcutaneous infusion, 60 mg q24h.
[f] Crush the tablets, put in a gelatin capsule, and place rectally.

TABLE 57-6. PHARMACOLOGICAL TREATMENT OF NAUSEA AND VOMITING

Metoclopramide is both a dopamine antagonist and a serotonin (5-HT4) agonist, but at doses greater than 120 mg a day, it becomes a serotonin (5-HT3) antagonist (62). It is very useful as an antiemetic and a prokinetic agent for gastroparesis-induced vomiting but caution must be exercised with older patients as it may cause extrapyramidal reactions that may not be dose dependent (59).

Anticholinergic medications are most efficacious in NV related to colic and mechanical bowel obstruction (58,59). They include scopolamine, hyoscyamine, and glycopyrrolate. Antihistamines are effective in motion sickness, mechanical bowel obstruction, and increased intracranial pressure. These drugs comprise buclizine, meclizine, and diphenhydramine.

Corticosteroids have a synergistic effect with metoclopramide and the serotonin antagonists (59) but are rarely useful as single agents (although they may reduce peritumor edema of gastrointestinal malignancies and brain metastases, and in so doing, lessen emetic episodes). Dexamethasone is the favored agent due to the small pill size, minimal mineralocorticoid activity, and availability of intravenous and subcutaneous administration. Serotonin antagonists are relatively new and expensive agents. Although quite useful in chemotherapy-induced emesis, their value in terminal NV is unknown. Nevertheless, they are frequently utilized in dying patients and are reportedly quite effective in reducing emesis, particularly NV associated with radiation, bowel obstruction, and renal failure (59,63).

Octreotide is a somatostatin analogue that is useful in reducing NV associated with intestinal obstruction. This drug decreases gastrointestinal secretions, stimulates absorption of water and electrolytes, and inhibits intestinal peristalsis (64).

Dronabinol is the only commercially available cannabinoid available in the United States. It is rarely used in terminal NV. It exhibits antikinetic properties in the stomach and small bowel (59) and may be most useful in emesis related to small bowel obstruction. It may, however, potentially worsen gastroparetic conditions.

The benzodiazepines have little role as singular antiemetics in the actively dying patient unless anxiety is a dominant component. They are best utilized as adjuncts to other antiemetics through their amnesic, anxiolytic, and sedative properties (65).

Many hospice programs utilize compounding pharmacists to prepare diverse and innovative medications and delivery systems for symptom control in dying patients. A compounding pharmacist can prepare a topical gel and/or suppository variously known as ABHR, ABHRD, or ABHRDC that contain commercially available antiemetics, including Ativan, Benadryl, or Dramamine, Reglan, Haldol, Decadron, and Cogentin. These drugs are combined in various dosages (i.e., Ativan, 1.0 mg; Benadryl, 12.5–25.0 mg or Dramamine, 25–50 mg; Haldol, 0.5–1.0 mg; Reglan, 5–10 mg; Decadron, 10 mg; and Cogentin, 1 mg). The suppositories have been quite useful in refractory NV and may be very effective in patients near death. Although there have been no studies that assess the varied combinations, they appear to benefit some patients because of both antiemetic and sedative effects.

PAIN

As death approaches, pain may become less problematic because the patient becomes bedbound and experiences less movement-related pain. Nevertheless, opioids must not be stopped abruptly, and clinicians should be cognizant that patients may be disturbed by pain even when comatose (7). Assessment of pain may become difficult and, in the final hours of life, patients may appear to show signs of pain when turned or repositioned, even when unconscious. Such pain may be due to an underlying medical disorder or joint stiffness secondary to bed rest and minimal body movement (66).

Assessing pain in confused or demented patients may be problematic. Such patients frequently exhibit pain by facial grimacing, resistance to turning or repositioning, agitation, and a reduction in functional abilities. Conversely, signs of apparent discomfort may be noted when a patient that is hearing or visually impaired or confused is touched without forewarning. Such response may not in fact be pain but rather the result of a startled response from tactile stimulation without prior warning.

In the final hours of life, patients may be unable to swallow, and sublingual/buccal, transdermal, rectal, intravenous, or subcutaneous administration of analgesics may be necessary (Table 57-7). Although rectal administration of sustained-release opioids is not approved by the U.S. Food and Drug Administration, studies suggest that rectal absorption is similar to oral administration. In addition, suppositories are available for nonsteroidal anti-inflammatory drugs, the tricyclic antidepressant doxepin, and the corticosteroid dexamethasone. The antiepileptics carbamazepine and valproic acid are frequently administered rectally by placing them in gelatin capsules.

Opioids that can be delivered subcutaneously	
Morphine	
Hydromorphone	
Methadone	
Fentanyl	
Opioids that can be delivered topically	
Fentanyl[a]	
Morphine[b]	
Oral opioids that can be delivered rectally	
Morphine[c]	
Oxycodone	
Anesthetics that can be delivered subcutaneously	
Lidocaine[d]	
Adjuvant medications and alternative routes of delivery	
Dexamethasone	s.q., i.m., i.v., p.r.
Indomethacin	p.r.
Diclofenac	p.r.
Ketorolac[e]	s.q.
Carbamazepine[f]	p.r.
Valproic acid	p.r.
Doxepin	p.r.

[a] Available as a topical patch, to convert from an oral opioid, convert the opioid to a morphine equivalent dose, then divide the morphine dose by 2 to get the approximate strength of the fentanyl patch. From Storey P, Knight EP, UNMC Hice. assessment and treatment of pain in the terminally ill. Asheville, FL: American Academy of Hospice and Palliative Medicine, 1996, with permission.
[b] Also available as a suppository; hydromorphone also available as a suppository.
[c] Morphine can be compounded into a gel for topical use, bioavailability is unknown.
[d] 1–3 mg/kg bolus; 100 mg/l i.v. over 20–30 min or s.q. over 30–60 min. If pain relieved, start an infusion either i.v. or s.q. at 0.5–2 mg/kg/h; serum levels may be monitored. See Ferrini R. Parenteral ketorolac for severe intractable pain in six hospice patients controlled at home. J Pain Symptom Manage 2000; 19:174–182.
[e] Can be administered by a continuous subcutaneous infusion, 60 mg q24h.
[f] Crush the tablets, put in a gelatin capsule, and place rectally.

TABLE 57-7. ALTERNATIVE ROUTES OF DELIVERY FOR PHARMACOLOGICAL TREATMENT OF PAIN

Unfortunately many patients and family members are reluctant to utilize the rectal route for administration of medications, especially if pain is not controlled and frequent supplementary doses of analgesics are required. In such cases, subcutaneous infusions are appropriate and well tolerated. Opioids; the nonsteroidal

anti-inflammatory ketorolac (67); the anticholinergics scopolamine, atropine, hyoscyamine, and glycopyrrolate; and the corticosteroid dexamethasone can all be given by means of the subcutaneous route in an effort to maintain or improve pain control. Epidural and other invasive analgesic interventions are rarely utilized when the patient is near death and should ideally be considered for use earlier in the disease process.

PALLIATIVE SEDATION

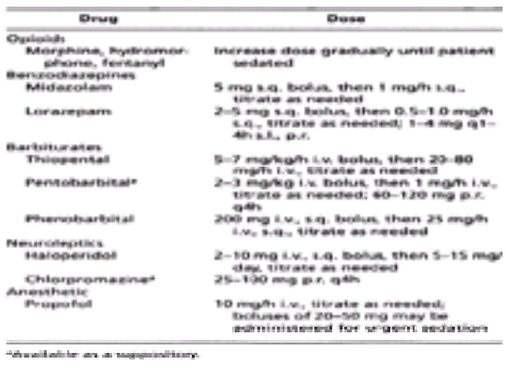
Palliative sedation, also referred to as terminal sedation, is the intentional use of pharmacological agents to induce and maintain a deep sleep, but not deliberately cause death, in specific clinical circumstances complicated by refractory symptoms (68). The incidence of PS varies from 5% to 52% (69). This variation is attributable to diverse definitions of PS, the retrospective nature of studies, and cultural and ethnic diversity. A refractory symptom is at times subjective and nonspecific and includes physical as well as psychological symptoms (70). Cherny and Portenoy clarify the boundaries of a refractory symptom by offering three criteria that suggests a symptom is refractory: (a) it cannot be controlled adequately despite aggressive efforts to identify a tolerable therapy that does not compromise consciousness, (b) additional invasive and noninvasive interventions are incapable of providing adequate relief, and (c) the therapy directed at the symptom is associated with excessive and intolerable acute or chronic morbidity and is unlikely to provide relief within a tolerable time frame (68).

The ethical validity of PS derives from the doctrine of double effect, a doctrine that is applied to situations in which it is impossible for a person to avoid all harmful actions, and the precept of informed consent. The traditional formulations of the doctrine of double effect involves four basic conditions: (a) the nature of the act must be good or morally neutral and not in a category that is absolutely prohibited and intrinsically wrong, (b) the intent of the clinician must be good, and the good effect, not the bad effect, must be intended, (c) the demarcation between the means and effects must be acceptable, in other words, the bad effect must not be the means to the good effect, and (d) proportionality, whereby the good effect must exceed or balance the bad effect (71).

Contentious issues with PS revolve around the use of tube feedings and eventual dehydration, and PS's relationship to physician-assisted suicide and euthanasia. Opponents of PS claim that the sedated patient dies of malnutrition and/or dehydration, not the underlying disease, although most patients have stopped eating and drinking prior to the initiation of PS, negating the argument of clinician-induced food and fluid deprivation. Nevertheless, if patients or surrogate family members wish to continue tube feedings, most clinicians discuss the futility of nutritional support but acquiesce to such requests and initiate PS.

Opponents of PS also contend that PS is nothing more than slow euthanasia. As proffered by the doctrine of double effect, however, the intent of the clinician must be considered. In the case of refractory symptoms, the intent is to alleviate suffering, not assist in suicide or euthanasia, even though PS may undeniably hasten death. Auspiciously, the U.S. Supreme Court fundamentally sanctioned PS in its decision opposing the constitutional right to physicianassisted suicide in 1997 (72,73), and in so doing, helped establish its value in the palliative armamentarium.

If PS is employed in a dying patient, informed consent must be obtained, as it is intimately integrated with autonomy and self-determination, and allows a reasonable person or surrogate to make independent and noncoerced treatment decisions. The reason for PS should be documented, as should the people present during the discussion, and if required by institutional or corporate policy, a completed consent form placed in the patient's chart. The choice of medications for PS is practitioner-dependent; clinicians should choose the drugs they are most familiar with, considering efficacy, cost, and clinical circumstance. Drugs frequently used for PS include opioids, benzodiazepines, barbiturates, neuroleptics, and propofol (Table 57-8).



Drug	Dose
Opioids	
Morphine, hydromorphone, fentanyl	Increase dose gradually until patient sedated
Benzodiazepines	
Midazolam	5 mg s.q. bolus, then 1 mg/h s.q., titrate as needed
Lorazepam	2–5 mg s.q. bolus, then 0.5–1.0 mg/h s.q., titrate as needed; 1–4 mg q1–4h s.l., p.r.
Barbiturates	
Thiopental	5–7 mg/kg/h i.v. bolus, then 20–80 mg/h i.v., titrate as needed
Pentobarbital*	2–3 mg/kg i.v. bolus, then 1 mg/h i.v., titrate as needed; 40–120 mg p.r. q4h
Phenobarbital	200 mg i.v., s.q. bolus, then 25 mg/h i.v., s.q., titrate as needed
Neuroleptics	
Haloperidol	2–10 mg i.v., s.q. bolus, then 5–15 mg/day, titrate as needed
Chlorpromazine*	25–100 mg p.r. q4h
Anesthetic	
Propofol	10 mg/h i.v., titrate as needed; boluses of 20–50 mg may be administered for urgent sedation

*Unavailable as a suppository.

TABLE 57-8. MEDICATIONS FOR PALLIATIVE SEDATION

FAMILY VIGIL

As death nears, family members tend to gather for comfort, solace, and support of themselves and their dying loved one. Emotions may become capricious and volatile, and aggressive treatments may be requested in an attempt to delay or preclude death. A “long-lost” family member may also suddenly appear and precipitate dissension among family members. Such disruption can distract health care providers as well as family members from providing the care and sustenance the dying patient needs. The clinician must keep in mind that such actions are often a manifestation of grief and fear, a desire to control an uncontrollable situation, or apprehension regarding one's own predestined death. It is important to maintain open communication with family members and reaffirm the goal of comfort care. Social work, nursing, and chaplain involvement can help direct family members in accepting the inevitable death of their loved one and provide reassurance that they will be there during this final journey.

Involving family members in the plan of care for the patient will enhance cooperation and a sense of contribution. They should be encouraged to assist in care by swabbing the oral mucosa, applying cool compresses to the eyes, performing gentle range of motion, and holding the hand of their loved one. The signs and events of the dying process should be reinforced, and personal, cultural, and religious beliefs and rituals honored (74,75). Family members may also be encouraged to convey the five affirmations recommended by Ira Byock: I forgive you, forgive me, I love you, thank you, and good-bye (76). Facilitating and supporting the opportunity for resolution and closure, personal and spiritual growth, and emotional healing is cardinal to a constructive death and bereavement, and should be provided for and encouraged.

To preclude confusion and turmoil during a home death, family members should be advised not to call “911.” Specific instructions should be given about whom to call (i.e., hospice nurse, social worker, chaplain, or physician). Family members should also be instructed about the physiological events that occur as the patient dies [e.g., the heart stops beating, breathing stops, pupils may dilate, eyes may remain open, urine and stool may be released, jaw may drop open (74)] and offered sufficient time to ask questions. Once death occurs, there is no immediacy to deliver the body to the morgue or funeral home, and family members should be allowed private time with their deceased loved one. Intravenous lines and catheters should be removed and, if desired by the spouse or children, the deceased bathed by family members; the latter can facilitate closure and allow expressions of immediate grief in a supportive setting (75). Finally, if the clinician is present to pronounce the patient, forthright and candid respect should be shown to the patient and family. Words such as, “I'm sorry, he/she has died,” and “My deepest condolences” are appropriate. However, silence, touch, and mere presence can be the greatest forms of communication and compassion at the time of death.

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58

SPIRITUALITY

CHRISTINA M. PUCHALSKI

Dying is a normal part of life. In today's society, however, dying is still treated as an illness. All too often, people die in hospitals or nursing homes, alone and burdened with unnecessary treatment. In many cases, treatments would be refused if patients were given the chance to talk about their choices with their physicians long before the deathbed scene. Dying people are not always listened to … their wishes, their dreams, their fears go unheeded. They want to share those with us.

At the turn of the century, an average American's life expectancy was 50 years (1). Now, 73% of deaths are among people at least 65 years old, and 24% of deaths are among those at least 85 years old. The leading causes of deaths in 1900 were influenza, tuberculosis, diphtheria, heart disease, cancer, and stroke. Today, heart disease is the number one cause of death, followed by cancer and stroke. Modern med-icine has granted more people an old age, but it also slows the process of dying. The end of life can last several years.

Because the end of life can last so long, the question arises as to how to live with dying. Some people choose to live fighting their illness to the end, with much of their focus on the fight. Others focus their attention on other aspects of their lives, such as work, family, and hobbies. Still others pursue a mix of these approaches. Each person's way of handling his or her dying is reflective of who that person is, what is important to him or her, and how he/she faces crisis. One needs to remember that there is no set map for living with dying. Each individual patient creates his or her own path and approach.

Illness and the prospect of dying can call into question the very meaning and purpose of a person's life. Illness can also cause people to suffer deeply. Victor Frankl wrote that man is not destroyed by suffering; he is destroyed by suffer-ing without meaning (2). Writing about concentration camp victims, he noted that survival itself might depend on seeking and finding meaning. Harold Kushner also noted that pain may be the reason, and out of pain and suffering may come the answer (3). In my own clinical experience, I have found that people may cope with their suffering by finding meaning in it. Illness can present people with the opportunity to find meaning in their lives. Many patients say that out of their despair they were able to realize an entirely new and more fulfilling meaning in their lives. Rabbi Cohen wrote:

> When my mother died, I inherited her needlepoint tapestries. When I was a little boy, I used to sit at her feet as she worked on them. Have you ever seen needlepoint from underneath? All I could see was chaos; strands of thread all over with no seeming purpose. As I grew, I was able to see her work from above. I came to appreciate the patterns, the need for the dark threads as well as the light and gaily colored ones. Life is like that. From our human perspective, we cannot see the whole picture, but we should not despair or feel that there is no purpose. There is meaning and purpose even for the dark threads, but we cannot see that right away. (4)

Spirituality helps people find hope in the midst of despair. As caregivers, we need to engage our patients on that spiritual level (5). This is where spirituality plays such a critical role—the relationship with a transcendent being or concept can give meaning and purpose to people's lives, to their joys and to their sufferings. Spirituality is concerned with a transcendental or existential way to live one's life at a deeper level, “with the person as human being” (6). All people seek meaning and purpose in life; this search may be intensified when someone is facing death.

Downey defined spirituality as “an awareness that there are levels of reality not immediately apparent and that there is a quest for personal integration in the face of forces of fragmentation and depersonalization” (7). Spirituality is that aspect of human beings that seeks to heal or be whole. Foglio and Brody wrote:

> For many people religion [spirituality] forms a basis of mean-ing and purpose in life. The profoundly disturbing effects of illness can call into question a person's purpose in life and work; responsibilities to spouse, children, and parents … Healing, the restoration of wholeness (as opposed to merely technical healing) requires answers to these questions. (8)

Healing, then, is not synonymous with recovery. Indeed, healing may occur at any time, independent of recovery from illness. In dying, for example, restoration of wholeness may be manifested by a transcendent set of meaningful experiences while very ill. It may be reflected by a peaceful death. In chronic illness, healing may be experienced as the acceptance of limitations (5). A person may look to medical care to alleviate his or her suffering, and when the medical system fails to do so, begin to look toward spirituality for meaning, purpose, and understanding. As people are faced with serious illness or the prospect of dying, questions often arise (9):

- Why did this happen to me?
- What will happen to me after I die?
- Why would God allow me to suffer this way?
- Will I be remembered?
- Will I be missed?

These questions can cause people to undergo a life review whereby they analyze their lives, accomplishments, relationships, and perceived failings (10). This questioning can result in fears, anxieties, and unresolved feelings, which in turn can result in despair and suffering as people face themselves and their eventual mortality. Cassell wrote: “Since in suffering, disruption of the whole person is the dominant theme, we know of the losses and their meaning by what we know of others out of compassion for their suffering” (11). Compassion is essential in the care of all patients, particularly those who are dealing with chronic and serious illnesses and are dying. Two Latin words form the root of the word compassion: “cum,” meaning “with,” and “passio,” meaning “suffering with” (12). What compassionate care asks us to do is to suffer with our patients, i.e., to be present to them fully as they suffer and to partner with them in the midst of their pain.

Medicine has enjoyed tremendous technological advances that have helped treat illness and prolong lives. These advances have shaped medical care in the Western world. Although this is very positive, it has tended to focus care on the technological and curative aspects, diminishing the importance of the humanitarian and compassionate aspects of care. As Doka wrote, “Efforts to humanize patient care are essential if the integrity of the human being is not to be obscured by the system” (6).

Dying is a natural occurrence in life. However, the Western medical and social culture still treats dying as if it were just a biological occurrence. Dying should be as natural an experience as birth. It should be a meaningful experience for dying persons, a time in which they find meaning in their suffering and have all the dimensions of their experience addressed by their caregiver. These dimensions are the physical, psychological, social, and spiritual (Table 58-1).

Physical	Pain and other symptom management
Psychological	Anxiety and depression
Social	Social isolation, economic issues
Spiritual	Purpose and meaning, relationships with the transcendent, search for ultimate meaning, hope, reconciliation, despair

TABLE 58-1. THE DIMENSIONS OF THE DYING EXPERIENCE

Patients encounter all types of suffering—spiritual as well as physical. Cecily Saunders, the founder of St. Christopher's Hospice in London and of the Hospice movement, stated that one of the aims of hospice is that there be relief of “total pain,” including the physical, emotional, psychological, social, and spiritua1 (13). It should be the obligation of all physicians and other caregivers to respond to, as well as attempt to relieve, all suffering if possible. Because people may cope with suffering using their spiritual resources, physicians should be able to communicate with their patients about spiritual issues. They should recognize the spiritual as well as physical dimensions of suffering and make resources available for those patients who wish them. Physicians have the responsibility to listen to people as they struggle with their dying. We *need* to be willing to listen to their anxieties, their fears, their unresolved conflicts, their hopes, and their despairs. If people are stuck in despair, they will suffer deeply. It is through their spirituality that people become unstuck from despair.

SPIRITUALITY IN CLINICAL PRACTICE

Medical professionals are recognizing that there are inadequacies in the health care system in terms of care of the dying. The American College of Physicians convened an end-of-life consensus panel, which concluded that physicians should extend their care for those with serious medical illness by attentiveness to psychosocial, existential, or spiritual suffering (14). Other national organizations have also supported the inclusion of spirituality in the clinical setting. The Joint Commission on Accreditation of Healthcare Organizations has a policy that states: Pastoral counseling and other spiritual services are often an integral part of the patient's daily life. When requested, the hospital provides, or provides for, pastoral counseling services (15).

The interest in spirituality in medicine among medical educators has been growing exponentially. Medical schools are now teaching courses in end-of-life care and in spirituality and medicine. Only one school had a formal course in spirituality and medicine in 1992. Now, over 70 medical schools are teaching such courses (16,17). The key elements of these courses have to do with listening to what is important to patients, respecting their spiritual beliefs, and being able to communicate effectively with them about these spiritual beliefs, as well about their preferences at the end of life.

In 1998, the Association of American Medical Colleges (AAMC), responding to concerns by the medical professional community that young doctors lacked these humanitarian skills, undertook a major initiative—The Medical School Objectives Project (MSOP)—to assist medical schools in their efforts to respond to these concerns. The report notes that “Physicians must be compassionate and empathetic in caring for patients … they must act with integrity, honesty, respect for patients' privacy and respect for the dignity of patients as persons. In all of their interactions with patients they must seek to understand the meaning of the patients' stories in the context of the patients', and family and cultural values” (18). In recognition of the importance of teaching students how to respect patients' beliefs, AAMC has supported the development of courses in spirituality and medicine.

In 1999, a consensus conference with AAMC was convened to determine learning objectives and methods of teaching courses on spirituality, cultural issues, and end-of- life care. The findings of the conference were published as Report III of the MSOP. This report included a clinically relevant definition of spirituality: Spirituality is recognized as a factor that contributes to health in many persons. The concept of spirituality is found in all cultures and societies. It is expressed in an individual's search for ultimate meaning through participation in religion and/or belief in God, family, naturalism, rationalism, humanism, and the arts. All of these factors can influence how patients and health care professionals perceive health and illness and how they interact with one another (19).

Spirituality, that which gives us meaning, can be expressed in many ways. When approaching patients' spiritual issues, it is important to recognize that the definition of spirituality is broad and all-encompassing. It is critical to allow the patient to inform the physician and other care providers what spirituality means to that patient. The outcome goals stated in MSOP III are that students will

- Be aware that spirituality, as well as cultural beliefs and practices, are important elements of the health and wellbeing of many patients
- Be aware of the need to incorporate awareness of spirituality, and cultural beliefs and practices, into the care of patients in a variety of clinical contexts
- Recognize that their own spirituality, and cultural beliefs and practices, might affect the ways they relate to, and provide care to, patients
- Be aware of the range of end-of-life care issues and when such issues have or should become a focus for the patient, the patient's family, and members of the health care team involved in the care of the patient
- Be aware of the need to respond not only to the physical needs that occur at the end of life, but also to the emotional, sociocultural, and spiritual needs that occur (19)

More than half of U.S. medical schools have courses in spirituality and medicine, many of which are required and integrated into the curriculum. The response to these courses has been positive. Students and practicing physicians find their relationships with their patients are warmer, more meaningful, and deeper once they talk with their patients about their spiritual beliefs. Medical students and residents are finding it easier to address end-of-life issues in the context of a spiritual history (20). Doctors who felt burned out by the hectic schedules of managed care now feel a way to reconnect with their patients and bring compassionate care giving back into the practice of medicine. Most important, the patients are happier because their whole person is treated—body, mind, and spirit—and not just their illness.

In these courses, future doctors learn how to communicate with patients about the patients' spiritual beliefs. A spiritual history is really nothing more than listening to the patient—to the patient's fears, hopes, and beliefs (21). When talking with someone about spiritual beliefs, it is natural to bring up issues of advance directives. Advance directives may be obtained through forms or brief questions in a history, which can be sterile and out of context. Discussions about the way people want to die should be done in the context of a person's values and beliefs. A spiritual history is an ideal place for centering discussions around advance directives (21).

DATA DEMONSTRATING PATIENT NEED

That spirituality is central to the dying person is well recognized by many experts, the most important of which are our patients. Several other national surveys have documented patients' desire to have spiritual concerns addressed by their physicians. A 1990 Gallup poll showed that religion, one expression of spirituality, plays a central role in the lives of many Americans (22). A more recent Gallup survey showed that 94% of Americans surveyed espouse a belief in God or a higher power, six out of ten Americans say that religion is very important in their life, and another three out of ten say it is fairly important. Approximately two-thirds of Americans claim to be a member of a church or synagogue. Additionally, when asked to state their religious preference, only 9% of the public says “none” (23).

The need for attentiveness to the spiritual concerns of dying patients has been well recognized by many researchers (24,25). A survey conducted in 1997 by the George H. Gallup International Institute showed that people overwhelmingly want their spiritual needs addressed when they are close to death. In the preface to the survey report, George H. Gallup, Jr., wrote: “The overarching message that emerges from this study is that the American people want to reclaim and reassert the spiritual dimensions in dying” (26). In the study, survey respondents said they wanted warm relationships with their providers, to be listened to, to have someone to share their fears and concerns with, to have someone with them when they are dying, to be able to pray and have others pray for them, and to have a chance to say goodbye to loved ones. When asked what would worry them, they said not being forgiven by God or others, or having continued emotional and spiritual suffering. When asked about what would bring them comfort, they said they wanted to believe that death is a normal part of the life cycle and that they would live on, either through their relationships, their accomplishments, or their good works. They also wanted to believe that they had done their best in their life and that they will be in the presence of a loving God or higher power. It is as important for health care providers and other caretakers to talk with patients about these issues as it is to address the medical-technical side of care.

The 1990 Gallup survey found that 75% of Americans say religion is central to their lives; a majority feel that their spiritual faith can help them recover from illness (22). Additionally, it was found that 63% of patients surveyed believe it is good for doctors to talk to patients about spiritual beliefs (27). Lehman and colleagues found that 94% of patients with religious beliefs agreed that physicians should ask them about their spiritual beliefs if they become gravely ill; 45% of patients who denied having any religious beliefs still agreed that physicians should ask their patients about their spiritual beliefs (28). In this survey, 68% of patients said they would welcome a

spiritual question in a medical history; only 15% said they actually recalled being asked by their physicians whether spiritual or religious beliefs would influence their decisions. A study surveying more than 200 hospital inpatients found that 77% believed physicians should consider patients' spiritual needs. Furthermore, 37% wanted their physician to discuss spiritual beliefs with them more frequently and 48% wanted their physicians to pray with them (29). A Time/CNN poll found that 65% of people surveyed want their physicians to address their spiritual issues (30). In a *USA Today Weekend* health survey, the majority of people polled felt that doctors should talk with their patients about spiritual concerns, yet only 10% reported that their doctors had discussed such issues with them (27). This latter statistic is understandable because spirituality has frequently been overlooked in medical school curricula and in the standards of medical care.

DATA DOCUMENTING THE RELATIONSHIP BETWEEN SPIRITUAL BELIEFS AND ILLNESS

There is a growing body of evidence documenting the relationship between patients' religious and spiritual lives and their experiences of illness and disease (31). In addition to surveys demonstrating that spirituality is important to people and that a significant percentage of patients would like their physicians to discuss their spiritual beliefs with them, a number of studies show that having spiritual beliefs is beneficial to patients, particularly those with serious illnesses. Reviews of the literature indicate potential relationships between measures of religious commitment and health measures, including morbidity and mortality, in studies of many diseases (32,33,34 and 35). Research suggests that mortality is reduced after cardiac surgery among those who receive comfort and support from religion (36).

Spirituality has been found to be an important factor in bereavement. It has been reported that parents who have lost a child have found much support in spiritual beliefs after their child's death (37). Spirituality is important in coping with pain and with dying. Ninety-three percent of patients with gynecologic cancers noted that their spiritual beliefs helped them cope with their cancer (38). Patients with advanced cancer who found comfort from their spiritual beliefs were happier, more satisfied with their lives, and had diminished pain (39). In a questionnaire sent out by the American Pain Society, prayer was the second most common method of pain management after oral pain medications, and the most common nondrug method of pain management (Table 58-2) (40).

Personal prayer is the most commonly used nondrug method for pain management.
Pain pills, 82%.
Prayer, 76%.
Pain i.v. medication, 66%.
Pain injections, 62%.
Relaxation, 33%.
Touch, 19%.
Massage, 9%.

TABLE 58-2. PAIN QUESTIONNAIRE BY AMERICAN PAIN SOCIETY TO HOSPITALIZED PATIENTS

In a study of patients with human immunodeficiency virus (HIV), those who were spiritually active had less fear of death and less guilt about their illness. Fear of death was more likely among the 26% of religious patients who felt their illness was a punishment from God. Fear of death diminished among patients who had regular spiritual practices or who stated that God was central to their lives. Patients who believed in God's forgiveness were more likely to engage in discussions about advance directives (41).

Quality-of-life instruments used in end-of-life care try to measure an existential domain, which addresses purpose, meaning in life, and capacity for self-transcendence. In studies of one such instrument, three items have been found to correlate with good quality of life for patients with advanced disease: if the patient's personal existence is meaningful; if the patient finds fulfillment in achieving life goals; and if life to this point has been meaningful (42). This supports the importance of addressing meaning and purpose in a dying person's life.

Writings on addiction also have supported the importance of finding meaning. The 12-step program Alcoholics Anonymous, one of the best known programs in the treatment of addiction, lists one of the 12 steps (which were described by some of the earliest members of the group) as “[we] came to believe that a power greater than ourselves could restore us to sanity” (43). In this view, addicts see their drug of choice as central in their lives; recovery hinges on the ability to find a meaning and purpose outside of oneself and one's illness.

The observations noted in patient stories (6,9) and in the writings of Foglio and Brody (8)—that illness can cause people to question their lives, their identities, and what gives their life meaning—is supported by research. For example, in a study of 108 women undergoing treatment for gynecological cancer, 49% noted becoming more spiritual after their diagnosis (38). In a study of parents with a child who had died of cancer, 40% of those parents reported a strengthening of their own spiritual commitment over the course of the year before their child's death (37). Illness, facing one's mortality, is an opportunity for new experience, self-awareness, and meaning in life.

Religion and religious beliefs can play an important role in how patients understand their illness. In a study asking older adults about God's role in health and illness, many respondents saw health and illness as being partly attributable to God and, to some extent, God's interventions (44). Prayer, in this study, appeared to complement medical care rather than compete with it.

Meditation has been found to be a useful adjunct to conventional medical therapy for chronic conditions such as headaches, anxiety, depression, premenstrual syndrome, acquired immunodeficiency syndrome, and cancer (45).

How spiritual modalities contribute to health and recovery is unclear. Koenig (46) and his colleagues propose an immune-related mechanism that might mediate the stress response. In a study of 1700 older adults, they found that those attending church were half as likely to have elevated levels of IL-6, which is an interleukin associated with stress and disease. The authors hypothesize that religious commitment, and perhaps spiritual practices in general, may improve stress control through better coping mechanisms, richer social support, and strength of personal values and world view. Benson and colleagues have studied the relaxation response and have shown it to be beneficial in a number of conditions, including hypertension (47), cardiac arrhythmia (48), chronic pain (49), insomnia (50,51), and depression and anxiety (52). Indeed, in more recent work, they propose a mechanism mediated through neural processes and their coupling to constitutive nitric oxide that could explain on a biochemical and neurological basis the beneficial effects seen with the relaxation response and possibly with spiritual beliefs (53).

Pargament and colleagues have studied both positive and negative coping, and have found that religious experiences and practices, such as seeking God's help or having a vision of God, extends the individual's coping resources and are associated with improvement in health care outcomes (54). Patients showed less psychological distress if they sought control through a partnership with God or a higher power in a problem-solving way, if they asked God's forgiveness or were able to forgive others, if they reported finding strength and comfort from their spiritual beliefs, and if they found support in a spiritual community. Patients had more depression, poorer quality of life, and callousness towards others if they saw the crisis as a punishment from God, if they had excessive guilt, or if they had an absolute belief in prayer and cure and an inability to resolve their anger if cure did not occur. Pargament et al. have also noted that sometimes patients refuse medical treatment based on religious beliefs (55).

SPIRITUAL COPING

How does spirituality work to help people cope with their dying (Table 58-3)? One mechanism might be through hope. Spirituality and religion offer people hope, and help people find hope in the midst of the despair that often occurs in the course of serious illness and dying. Hope can change during a course of an illness. Early on, the person may hope for a cure; later, when a cure becomes unlikely, the person may hope for time to finish important projects or goals, travel, make peace with loved ones or with God, and have a peaceful death. This can result in a healing, which can be manifested as a restoration of one's relationships or sense of self. Often our society thinks in terms of cures. Whereas cures may not always be possible, healing—the restoration of wholeness—may be possible to the very end of life.

Hope: for a cure, for healing, for finishing important goals, for a peaceful death
Sense of control
Acceptance of the situation
Strength to deal with the situation
Meaning and purpose: in life, in midst of suffering

TABLE 58-3. SPIRITUAL COPING

Religious beliefs offer a sense of hope. For example, in Catholicism, hope in Jesus' promise of victory over death through resurrection and salvation gives Catholics hope in a life beyond death. In the funeral rites, it is stated: “I believe in the resurrection of the dead and the life of the world to come” (56). In the Protestant view, the concept of salvation in death gives hope. Jesus' dying and rising from the dead means that those who participate in His death no longer participate in the sinful human nature (57). In Eastern traditions such as Buddhism and Hinduism, the hope of rebirth and a belief in karma offer people hope in the face of mortality (58). In Judaism, there are many diverse ways of viewing death. For some, hope is found in living on through one's children. In the orthodox and conservative views, there is a belief in a resurrection in which the body arises to be united with the soul (59). For patients both with and without specific religious beliefs, there is a need to transcend death, which also may be manifested through living on through one's relationships or one's accomplishments and deeds (60). Irion suggests that humans may create abstractions by portraying a life after death (61). For the religious, this may take the form of concepts found in their religious traditions. For others, life after death might be in terms of one's descendants. For some, it might be being immortalized in the memory of others or in the contributions one makes in life. Cultural beliefs and traditions can also contribute to how people find meaning and hope in the midst of despair (62).

Spirituality can offer people a sense of control. Illness can disrupt life completely. Some people find a sense of control by turning worries or a situation over to a higher power or to God (63). Similarly, people can use their beliefs to help them accept their illness and find strength to deal with their situation (43,64,65). Reconciliation may be an important aspect of a dying person's spiritual journey. Often people seek to forgive others or themselves as they review their lives and their relationships. Finally, finding meaning and purpose in the midst of suffering is integral to spirituality.

SPIRITUAL CARE

Spiritual care at its essence is relational (Table 58-4). Spirituality can be defined as a relationship not only with the transcendent, but also with others. The connection that physicians, other health care providers, and families make with the ill and dying patient is, at its root, spiritual. The care that the physician provides is rooted in spirituality through compassion, hopefulness, and the recognition that, although a person's life may be limited or no longer productive, it remains full of possibility (66). Even though a person can no longer have curative therapy, he or she can still find meaning and purpose in life. Patients who are seriously ill can still have relationships, and they can still heal. The physician and other care providers can offer the opportunity for healing by being present to the patient. The patient and the physician (or other health care provider) connect with each other in the context of this healing relationship. Patients want to have warm, caring relationships with their physicians, as the Gallup survey suggests (26). There are studies that document the importance of the doctor-patient relationship (67,68,69,70,71,72 and 73). Dr. Francis Peabody wrote in his 1927 medical classic, *The Care of the Patient*t, “One of the essential qualities of the clinician is interest in humanity, for the secret care of the patient is in caring for the patient” (74). This relationship can have potential positive impact on health care outcomes, compliance, and patient satisfaction (67,71,72,75,76 and 77).

Practice of compassionate presence
Listening to patient's fears, hopes, pain, and dreams
Obtaining a spiritual history
Attentiveness to all dimensions of the patient and patient's family: body, mind, and spirit
Incorporation of spiritual practice as appropriate
Chaplains as members of the interdisciplinary health care team

TABLE 58-4. SPIRITUAL CARE

Spiritual care emphasizes the importance of a relationship between two people. The physician may be the professional expert in most of the encounter, but the physician is still a human being. By relating from our humanness, we can help to form deeper and more meaningful connections with our patients. This requires an awareness of the physician's own values, beliefs, and attitudes, particularly toward the physician's own mortality. By confronting one's own mortality, one can better understand what the patient is facing. Also, the stress of working with seriously ill and dying patients can be better handled by an attentiveness to one's own spiritual and values framework. Many physicians speak of their own spiritual practices and how those practices help them in their ability to deliver good spiritual care and, in fact, good medical care (5,78).

One of the key components of this relationship is the ability of the physician to be totally present to the patient, i.e., the practice of compassionate presence. This means that the physician brings his or her whole being to the encounter and places full attention on the patient, not allowing distractions, such as time pressures, focus on the biomedical aspects of treatment, or other thoughts, to interfere with that attention. Integral to this is the ability to listen to the patient's fear, hopes, and dreams and to be attentive to all dimensions of a patient's and their family's lives: the physical, emotional, social, and spiritual. Some physicians suggest that current medical practices do not allow enough time for this. However, being wholly present to the patient is not time dependent. It simply requires the intention on the part of the physician to be fully present for their patients.

Obtaining a spiritual history is one way to listen to what is deeply important to the patient (21). When one gets involved in a discussion with a patient about his or her spirituality, one enters the domain of what gives the person meaning and purpose in life and how that person copes with stress, illness, and dying. The spiritual history affords the patient the space and opportunity to address his or her suffering and hopes. Having the physician inquire about the patient's spiritual beliefs gives the patient an opening and an invitation to discuss spiritual beliefs, if that is what the patient would like to do. It also enables the physician to connect with the patient on a deep, caring level. In fact, many physicians who obtain spiritual histories remark that the nature of the doctor-patient relationship changes. As soon as they bring up these questions, they feel that it establishes a level of intimacy, an understanding of who the person is at a much deeper level than is typical. The relationship feels less superficial (21). Patients note that they feel more trusting of a physician who addresses and respects their spiritual beliefs. In one survey, 65% of patients in a pulmonary outpatient clinic noted that a physician's inquiry about spiritual beliefs would strengthen their trust in the physician (28).

Once the physician finds out what the patient's spiritual beliefs are, he or she can then address any spiritual practices that are important to the patient. These might be prayer, meditation, listening to certain music, enjoying solitude, or writing poetry. One can then incorporate these practices as appropriate. Chaplains and other spiritual care providers (spiritual directors, ministers, priests, rabbis, imans, music thanantologists, and others) are experts trained in the area of spirituality and religion. Working with these spiritual care providers is essential to holistic care. Chaplains should be integrated into interdisciplinary health care teams. Hospice teams often have chaplains as part of the care team.

ETHICAL ISSUES: ROLE OF SPIRITUALITY IN THE CLINICAL SETTING

It is critical for physicians and other health care providers to address spiritual issues with their patients because spirituality affects patients' clinical care in a direct

manner. Spiritual issues can impact clinical care in various ways, which are illustrated by the following cases.

Case 1

Spiritual beliefs may be a dynamic in patients' understanding of their illness. Julie was a 28-year-old woman whose husband left her recently. She learned through the family grapevine that he has acquired immunodeficiency syndrome. She came into a clinic and saw a physician for the first time to get tested for HIV. When she returned to the clinic for her test results, she found out that she was HIV positive. The physician attempted to present an optimistic picture by relaying all the newest information on treatment for HIV. The patient, however, continued to cry out about “God doing this to me.” The physician persisted in discussion of the medical and technical aspects of the diagnosis while the patient continued to make references to God. After some time, the physician asked the patient why she thought her illness was coming from God. She told the physician that she was raped as a teenager, got pregnant, and had an abortion. She said, “I have been waiting for the punishment for 15 years, and this is it.” The patient refused all medications and treatment.

Patients come to understand their health, illness, and dying through their beliefs, cultural backgrounds, past experience, and values. In this case, Julie had been carrying guilt for an event that happened many years before. The temptation for the physician was to alleviate this guilt by talking about how understandable the abortion was in the context of the rape. However, this is not what the patient felt, and by trying to erase her guilt, it actually precluded the patient from talking about her feelings. The physician instead listened to the patient and did not force the issue of medications and preventive care. The physician continued to see the patient regularly, listening to her issues around the diagnosis. She also referred Julie to a chaplain who worked further with Julie on these issues. It took approximately a year before Julie was able to see God as forgiving and was able to forgive herself. It was then that she could focus on the treatment of her HIV disease. Issues like these can be complicated. What part of Julie's beliefs came from strongly held religious dogma and what part from low selfesteem or depression? Chaplains are trained to understand the difference in the roots of these beliefs, and they are trained to help patients resolve these types of conflicts. In addition, physicians can be helpful by listening to patients, giving patients the time to resolve conflicts, and respecting patients' rights to their own beliefs.

Case 2

Religious convictions/beliefs may affect health care decision making. Frank was an 88-year-old man dying of pancreatic cancer in the intensive care unit. He was on pressors and a ventilator. The team approached the family about withdrawing support. The family was very religious and believed that their father's life was in God's hands; they believed there would be a miracle and that their father would survive.

These types of cases are very common and often are handled poorly. Physicians and intensive care unit teams get frustrated that patients' families can't see that their loved one is dying, and the family feels hurt and angry that the medical teams do not understand their beliefs. The discussion often gets polarized and difficult to resolve. It is critical that the medical teams, even if they do not agree with the family, respect family beliefs. Often, simply listening to the family about what they mean by a “miracle” can open up the conversation to many feelings that the family is experiencing. For example, the physician could simply say, “I can understand that a miracle would be wonderful,” and then wait to see what the family says. Or the physician could ask, “What does a miracle mean to you?” If families feel respected, they are not as likely to feel threatened and that the medical team opposes them. The medical team, in turn, can get to know the values and beliefs of the family. Referral to a chaplain would be critical in this case. The chaplain, someone who is not perceived as being a part of the medical team per se, can explore the issues of miracles in a very nonthreatening way.

In Frank's case, the chaplain worked with the family. Over time, they began to see the possibility of a miracle independent of whether their father was on a ventilator. The family was then at peace with withdrawing ventilator support. The family was invited to bring their minister in during the whole process, and there were prayers and rituals at the bedside. Their father lived for several days and then died at peace.

Case 3

Spirituality may be a patient need. Rebecca was a 60-year-old woman who had a stroke and had had diabetes and hypertension for many years. She was very debilitated, being wheelchair bound with a speech impediment. Her major coping strategy was prayer. She was Catholic. Her church group and family were her major social supports. It was very important for her to discuss her spiritual beliefs with her physician.

Rebecca's faith was central to her life and was the basis of all her decisions. It was the way she coped with the effects of her chronic illnesses and with her dying. It was important for her to talk about her faith at every visit. She had an inner strength that was rooted in her religious beliefs and enabled her to withstand numerous physical and emotional challenges. In the end, it was her faith that probably gave her the will to live beyond what medical statistics would have predicted for someone as ill as she was. Daily prayer was so important to her that it also became an indicator for her well-being. At one point in her illness, she became very depressed. Although she denied symptoms of depression, she related that she was too tired to pray. She was then able to recognize symptoms of depression. Her church group was also a strong support. In fact, they were so present to her that they were clearly part of her extended family.

Case 4

Spirituality may be important in patient coping. Ronda was a 54-year-old woman with advanced ovarian cancer. Her husband, who was her major support, died unexpectedly. Ronda, who was Jewish, dealt with her suffering and depression through her faith in God. She also joined Jewish Healing Services for support and guidance.

Ronda was raised Jewish but was not observant throughout her adult life. She described herself as an optimist and saw that attitude as an inner strength. Her will to live was strong, and her fight to survive her cancer in the face of dismal odds gave her meaning in life. She spoke of her cancer as a gift in that it gave her a new perspective of life. She came to understand her life in a different, deeper way. She expressed a sense of gratitude for being alive each moment of the day and did not take anything, or anyone, for granted. During times of stress and loss, she relied on her inner strength as a resource. She reached out to support networks, such as the Jewish Healing Services. When her cancer metastasized, she looked at her religious roots for an understanding of death and of suffering. It was important for her to talk with her physicians about these issues and for her to be respected. For a physician to dismiss her will to live and try new therapies simply because of a statistical understanding of her disease would be to dismiss who she is as a person, a “statistic of one,” as she said. It was important for her to be able to talk with her physician about her will to live and also about her search for meaning in the midst of suffering. She made a “dream list” as to what was important for her to accomplish before her death. Therapy was adjusted around her ability to complete her dream list.

Case 5

Spirituality may be integral to whole patient care. Joe was a 42-year-old man with irritable bowel syndrome. He had major stressors in his life, including a failed marriage and dissatisfaction at work. He had signs of depression, including insomnia, excessive worrying, decreased appetite, and anhedonia. Overall, he felt that he had no meaning and purpose in life.

Joe did not respond to medication and diet changes alone. However, with the addition of meditation and counseling, Joe improved. In this case, the physical, emotional, social, and spiritual issues all interplayed and affected how he coped with illness.

SPIRITUAL HISTORY

The main elements of a spiritual history that has been developed for physicians and other health care providers can be recalled by using the acronym “FICA” (21).

F—Faith and Belief

“Do you consider yourself spiritual or religious?” or “Do you have spiritual beliefs that help you cope with stress?” If the patient responds “no,” the physician might ask, “What gives your life meaning?” Sometime patients respond with answers such as family, career, or nature.

I—Importance

“What importance does your faith or belief have in your life? Have your beliefs influenced how you take care of yourself in this illness? What role do your beliefs play in regaining your health?”

C—Community

“Are you a part of a spiritual or religious community? Is this of support to you and how? Is there a group of people you really love or who are important to you?” Communities, such as churches, temples, mosques, or a group of likeminded friends, can serve as strong support systems for some patients.

A—Address/Action in Care

The physician and other health care providers can think about what needs to be done with the information the patient shared—referral to chaplain, other spiritual care provider, or other resource.

FICA is not meant to be used as a checklist, but rather as a guide as to how to start the spiritual history and what to listen for as the patient talks about his or her beliefs. Mostly, FICA is a tool to help physicians and other health care providers know how to open a conversation to spiritual issues and issues of meaning and value. In the context of the spiritual history, patients may relate those fears, dreams, and hopes to their care provider. The spiritual history can be done in the context of a routine history or at any time in the patient interview, usually as a part of the social history. In addition to religious or spiritual beliefs and values and other aspects of the spiritual history, the social history should address lifestyle, home situation, and primary relationships; other important relationships and social environment; work situation and employment; social interests/ avocation; life stresses; and lifestyle risk factors (e.g., tobacco, alcohol, or illicit drugs).

The spiritual history is patient-centered. One should always respect patients' wishes and understand appropriate boundaries. Physicians and other health care providers must respect patients' privacy regarding matters of spirituality and religion and should avoid imposing their own beliefs on the patient (79).

The following case illustrates how FICA can be used. A patient who died of metastatic malignant melanoma was an Episcopalian. Her religious beliefs were central to her life, and in fact, were the means through which she came to be at peace with dying. During her last hospitalization, the house officers caring for her were apprehensive about discussing advance directives and dying. However, during the spiritual history, the patient told them how her religious beliefs helped her come to terms with dying and how she was ready to die naturally. She handed them her living will. She also asked that her church members be allowed to visit her often. She later told me that being asked about her beliefs helped her feel respected and valued by the physicians and that she felt that she could trust them more. The physicians stated that once they asked a spiritual history, the nature of the interaction between themselves and this patient changed. It felt “more natural, more comfortable, warmer and more honest.”

Another case illustrates the variability encountered in practice. When asked “if you have any spiritual beliefs that help you with stress,” a patient undergoing a routine examination answered that she found meaning and purpose while sitting in the woods near her house—that nature brought her peace. This was very important to her, as she noted that on days when she did not meditate there in the morning, she would become scattered and tense. Her community consisted of a group of like-minded friends who shared her beliefs. She asked that her medical record indicate that when she became seriously ill or dying, she wanted a room in her hospice overlooking the trees. She also asked to learn basic meditation techniques. In a subsequent visit many months later, she reported that she had stopped meditating, with negative results; resuming meditation helped her cope better with her stress.

ETHICAL ISSUES: PROFESSIONAL AND PERSONAL BOUNDARIES

Performing a spiritual history has been included in coursework on spirituality and medicine (21). The spiritual history emphasizes the practice of compassion with one's patients, and helps the clinician learn to integrate patients' spiritual concerns into the therapeutic plans. Given the data suggesting that spirituality may be beneficial for patients who are coping with illness, health care institutions should have written policies stating that the patient has a right to express his or her spirituality and religiosity in a respectful and supportive clinical environment.

Physicians should strive to discuss patients' spiritual concerns in a respectful manner and as directed by the patient. The spiritual history is patient-centered, not physiciancentered (Table 58-5). A physician should always respect patients' privacy regarding matters of spirituality and religion, and must be vigilant in avoiding imposing his or her beliefs on the patients. The relationship between physician and patient is not an equal one. There is an intimacy in the relationship, but it is intimacy with formality. The patient comes to the physician in a vulnerable time of his or her life, often looking to the physician as a person of authority. The physician should not abuse that authority by imposing his or her own beliefs, or lack of beliefs, onto patients. A vulnerable patient may adopt a physician's belief simply because the patient is fearful and assumes the physician knows more. In terms of spiritual intervention, physicians can recommend a variety of interventions, such as chaplain referral, meditation, yoga, prayer, or other spiritual practice. But the decision to recommend these comes from the patient. For example, physicians could recommend religious and spiritual practices to a patient if these practices are already part of that patient's belief system. However, an agnostic patient should not be told to engage in worship any more than a highly religious patient should be criticized for frequent church attendance. Thus, if a patient states that prayer helps with stress, the physician could suggest that prayer might help in dealing with a serious diagnosis. Or, if a patient finds meaning and purpose in nature, a physician might suggest meditation techniques focused on nature.

Spiritual history: patient-centered
Recognition of pastoral care professionals as experts
Proselytizing is not acceptable in professional settings
More in-depth spiritual counseling should be under the direction of chaplains and other spiritual leaders
Praying with patients:
Not initiated by physicians unless there is no pastoral care available and the patient requests it
Physician can stand in silence as patient prays in his/her tradition
Referral to pastoral care for chaplain-led prayer

TABLE 58-5. ETHICAL AND PROFESSIONAL BOUNDARIES

Patients sometimes ask their physician about the physician's beliefs. Given the unequal relationship between patient and physician, it is important that the question be handled carefully and with the same guidelines that are used when addressing other sensitive issues such as sexual history or domestic violence. Patients sometimes ask personal questions of their physicians to take the attention off themselves. Sometimes, it is to see if they can connect with the physician by reassuring themselves that the physician has the same beliefs as they. In general, if asked about his or her own beliefs, the physician could ask the patient why it is important for him or her to know that information. The physician can reassure the patient that the focus of the encounter is on the patient's needs and issues, not the doctor's. In some cases, patients still feel the need to know. A patient of a certain religious belief may want to work only with a doctor of that same religion. In some cases, it may not be possible to accommodate the patient, but at least the physician can explore with the patient the reasons for the request. Some patients want to know that their beliefs will not be ridiculed. A response from the physician that he or she respects and supports a patient's beliefs might serve to reassure the patient. In general, it is best to avoid sharing one's personal beliefs unless one already knows the patient and is comfortable that this sharing would not coerce the patient into adopting the physician's beliefs or intimidate the patient from sharing more about his or her own beliefs. A physician should not do anything that violates his or her own comfort level as well. Many physicians prefer to keep their private lives private in the professional context of the doctor-patient relationship.

Patients often ask physicians to pray with them. A physician need not worry that it is somehow inappropriate to allow a moment of silence or a prayer if the patient requests this. In fact, walking away and not showing respect for the request may leave the patient with a sense of abandonment by the physician. If the physician feels conflicted about praying with patients, he or she need only stand by quietly as the patient prays in his or her own tradition. Alternatively, the physician could suggest calling in the chaplain or the patient's clergyperson to lead a prayer. Physician-led prayer is generally not recommended, as that is usually the role of the clergy or chaplain. In addition, having the physician lead a prayer opens the possibility of having the prayer be of the physician's belief, not of the patient's. Furthermore, clergy and chaplains are trained specifically in techniques of leading prayer in ecumenical and health care contexts.

Appropriate referrals to chaplains are important to good health care practice and are as appropriate as referrals to other specialists. Chaplains are clergy or laypersons certified in a pastoral training program designed to train them as chaplains. Chaplains work in hospital settings, outpatient clinics, businesses, schools, and prisons. They are trained to be spiritual care providers working with people to explore meaning in life, cope with suffering, and use their beliefs to help them cope with illness or stress. Chaplains work with people of all faiths, as well as with nonreligious people. Clergy are trained to provide religious care usually only to people of their specific

denomination.

Where are the boundaries between what chaplains do and what physicians do? Some would argue that discussions with patients about spiritual matters should be initiated solely by chaplains (80). Physicians can use spiritual histories as a screening tool. By inquiring about a patient's beliefs, the physician can evaluate whether the beliefs are helpful or harmful to the patient's health and medical care. If a patient has beliefs that support him or her and give meaning and peace of mind, the physician can encourage those beliefs. In cases in which spiritual beliefs interfere with a patient's getting needed therapy—for example, a patient who thinks an illness is a punishment caused by God and therefore refuses medicine or treatment because of a feeling that the punishment is deserved—a referral to a chaplain would be very helpful. Patients have the right to refuse medical treatment. However, it is important that the choice be made with full informed consent. Therefore, if a patient refuses treatment based on a religious or spiritual belief, it may be appropriate to refer the patient to a chaplain so that the chaplain can explore these beliefs with the patient.

Sometimes, refusal of treatment is based on accepted religious tenets. Other times, the patient may attribute the reasons for refusal to religious beliefs when it actually stems from other concerns, such as lack of self-esteem or depression. The chaplain is trained to explore the beliefs with the patient further and help the patient differentiate between the two. The physician should be respectful of the patient's beliefs, but still explain the consequences of refusal of treatment without being coercive. This way the patient can have enough medical and spiritual information to make a fully informed decision. Physicians in general are not trained to explore the theological aspects of belief, although they can listen and learn about belief from patients. However, physicians can listen to and support patients as they make decisions for themselves. Sometimes, simply listening to a patient in a nonjudgmental fashion and asking a few open-ended questions, such as “tell me more about your belief,” can help patients resolve issues of belief and treatment for themselves.

Although many studies suggest that spirituality can be helpful, there are also circumstances in which spirituality can have a negative effect on health. It is important for health care providers to recognize this dynamic. For example, a person who interprets his or her illness as a punishment from God might attempt to refuse treatment. In such a scenario, a chaplain or other religious advisor could perhaps work with the patient's beliefs to help him or her work through the guilt issues. The patient might accept treatment or refuse it, but at least the decision wouldn't be motivated solely by guilt, and would be more of an informed decision. Some people who feel guilt in their relationships with God might also relate to others in their lives in a similar way. Counseling may also be helpful. Some religious beliefs forbid certain medical practices, such as Jehovah's Witnesses' refusal to accept blood transfusions. It is important to recognize the difference between refusing treatment based on an established religious principle versus refusal of treatment stemming from depression, unwarranted guilt, or a misperceived sense of punishment from God. Some patients may have complicated ethical and spiritual issues. Physicians need not feel that they must solve these dilemmas on their own. Chaplains, members of ethics committees, and counselors often work with physicians in the care of patients.

It is important to recognize that spirituality in the health care setting is not in any one person's domain. Physicians, nurses, social workers, and chaplains all can deal with patient spirituality. It also is true, however, that most physicians are not trained to deal with complex spiritual crises and conflicts. Chaplains and other spiritual caregivers are. Therefore, it is important that physicians obtain a spiritual history as a way of inquiry about spiritual issues that might impact a patient but that physicians also recognize when to make a referral to these specialists.

NEUROTHEOLOGY

Patients may talk about spiritual or mystical experiences, which might manifest as visions, feeling God's or a deceased loved one's presence, altered states of consciousness, locutions, or sensory experiences (unusual smells, sights, or sounds). From the clinical standpoint, there is a debate as to the difference between spiritual experience and psychopathology. Many patients close to death talk of seeing loved ones or angels in the room. Some physicians medicate patients if these experiences cause distress or agitation. This assumes that spiritual experiences are comforting versus psychopathological ones, which may cause agitation. Theologians would argue that, in fact, not all spiritual experiences are comforting, and that medicating people in the midst of a spiritual experience might be in conflict with patients' beliefs and religious traditions.

There are no clear-cut answers to this dilemma. But there is a new area of research and study called neurotheology, the study of the neurobiology of religion and spirituality. By using brain-imaging studies, scientists are attempting to identify the brain's spirituality circuit. Results indicate that certain spiritual experiences, such as deep meditation or intense religious moments in prayer, can be associated with distinct neural activity in the brain. However, this does not mean that such experiences are mere neurological illusions, nor do these studies establish cause and effect. Andrew Newberg, a physician who does this research at the University of Pennsylvania, notes that “there is no way to determine whether the neurological changes associated with spiritual experience mean that the brain is causing those experiences or is instead perceiving a spiritual reality” (81).

Theologians suggest that neurotheologians identify religion with specific experiences and feelings. Spiritual or mystical experiences may be part of a person's life, but those experiences have nothing to do with how well people communicate with God nor with the spiritual practices inherent in religions, such as prayer or virtue. Neurotheologians suggest that we may be “wired for God” (45) or that evolution has programmed the brain to find pleasure in transcending the self. But most mystics and spiritual leaders write not so much of pleasure from spiritual practice as of the perseverance of a spiritual practice, which at times can be difficult and seemingly empty. Most mystics, such as Teresa of Avila, have seen spiritual practices as leading them beyond themselves to the practice of charity and love of neighbors (82). Teresa of Avila and other mystics regarded spiritual or mystical experiences as special gifts of God but not essential to spiritual growth. Furthermore, spiritual experiences do not indicate the level of charity or love present in the heart of the person—only external acts of charity do.

Neurobiologists can correlate certain experience with certain brain activity, but it would be reductionistic to conclude that the brain is the only source of the experience. For example, science cannot measure the influence of spiritual grace. Thus, in the clinical setting, it is important to recognize the limits of science and to relinquish the need for reductionistic explanatory models for spiritual beliefs and experiences. Much of what happens to our patients may have no answers. Illness causes us to ask questions that are deeply spiritual and unanswerable scientifically: Who am I? Why am I suffering? What is the meaning of my illness and suffering? Illness, in and of itself, is a spiritual journey, which may include emptiness, joy, despair, hope, and mystical experiences. As physicians and caregivers, our job is to support our patients as they go through this journey.

Although it is critical to respect professional boundaries and not try to do the chaplain's job, there is a spectrum along which most physicians can operate. Some physicians elect to pursue issues of religion or spirituality with a patient in greater depth than would others. Consider as an analogy the treatment of depression by an internist. Some internists treat simple cases of depression, referring only the more complex ones to psychiatrists. Others refer a patient to a psychiatrist immediately on diagnosis of depression. Each physician must be honest in recognizing his or her own professional and personal limitations. Ultimately, the goal is to do what is best for the patient. If early referral to a chaplain or other support person is in the best interest of the patient, then that is the appropriate course of action.

CARING FOR OUR PATIENTS

Beyond the data, writings, and courses are personal stories from physicians and their patients. In my own experience as a physician who cares for patients with chronic and terminal illnesses, I feel privileged and honored to care for people who are facing death. Their strength and courage in the midst of suffering is inspiring. My patients are greater teachers to me and to my students on life than any philosophical text. The stories they share are ones of personal transcendence, courage, and dignity. My patients continually live with dying and in the midst of that are often able to face their losses, their fears, and their pain, and transcend to a place where they see their lives as rich and fulfilling. They reprioritize and thus are able to find a place of deep meaning and purpose in their lives. It is often humbling to me to recognize that what I place importance on in life now may have little or no importance in the end, when facing my own mortality. My annoyance at rush hour traffic when I am late, or my emphasis on academic success, pales by comparison to my patients' descriptions of a glowing sunrise or the deep love they feel for another. I would encourage all students reading this text to look on your patients as teachers and to approach dying patients not with trepidation and fear but with openness to all the joy and wisdom you can experience with them.

We should have systems of care that allow for people to die in peace, to die the way they want to, and to be able to engage in those activities that bring peace to them: prayer, meditation, listening to music, art, journaling, sacred ritual, and relationships with others. Our systems of care should be interdisciplinary, with physicians, nurses, social workers, chaplains, and other spiritual care providers all working together to provide spiritual and holistic care for our patients. It is then that health care systems will become caring communities rather than impersonal, technologically driven ones.

Our culture and our profession as a whole must look at dying very differently from the way it currently does. We need to see dying not as a medical problem but as a natural part of life that can be meaningful and peaceful. We can broaden and perhaps even enhance our lives now by knowing that one day we will die. By thinking about our mortality early in life, we will not be caught off guard and pressured by the dilemmas of choices at the end of life. We will have had a chance to think about some of those choices sooner and to come to peace with our mortality. This is where religious organizations can be particularly helpful. They can facilitate our discussions of dying and what that means to us. They can educate their members about the importance of preparing themselves for the choices, both spiritual and medical, that need to be made near the end of life. We, the interdisciplinary care team, can jointly assist the dying person come to peace in life's last moments.

All of us, whether actively dying or helping care for the dying, have one thing in common: We all will die. The personal transformation that is often seen in patients as they face death can occur in all of our lives. By facing our inevitable dying we can ask ourselves the same questions that dying patients face—what gives meaning and purpose to our lives, who we are at our deepest cores, and what the important things are that we want to do in our lives. By attending to the spiritual dimensions of our

personal and professional lives, however we express that, we can better provide care to our patients (83).

Wayne Muller has written:

> There are times in all of our lives when we are forced to reach deep into ourselves to feel the truth of our real nature. For each of us there comes a moment when we can no longer live our lives by accident. Life throws us into questions that some of us refuse to ask until we are confronted by death or some tragedy in our lives. What do I know to be most deeply true? What do I love, and have I loved well? Who do I believe myself to be and what have I placed on the center of the altar of my life? Where do I belong? What will people find in the ashes of my incarnation when it is over? How shall I live my life knowing that I will die? And what is my gift to the family of earth? (84)

Of all life's difficult yet important experiences, dying may be the most difficult one we will ever have. The moment of death, and the dying that precedes it, brings to a close the journey that each one of us has been on. We are the privileged persons who attend people while they are dying, be they our patients or our loved ones and friends. We are the persons who can bring hope and comfort to dying patients as they complete their lives. We need to ensure that our society and our systems of care preserve and enhance the dignity of all people, especially when they are made vulnerable by illness and suffering. We need to listen to the dying and to all our patients, and be with them, for them. The process of dying can be a meaningful one, one that we can all embrace and celebrate rather than fear and dread.

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59

BEREAVEMENT CARE

J. WILLIAM WORDEN

DEFINITIONS

Bereavement: the situation of losing to death a person to whom one is attached.

Mourning: the process that one goes through adapting to such a loss.

Grief: the thoughts, feelings, and behaviors one experiences after the loss.

Bereavement care should be a part of any comprehensive palliative care program. The well-being of the family and of others who are close to a dying or recently deceased person is part of the health professional's responsibility. Health care providers and the institutions they serve must understand the impact of grief and be sensitive to the needs of the bereaved by offering both support and information (1). Included in the understanding of bereavement must be an awareness of the negative consequences that can accrue to survivors after a death. Bereavement is not in and of itself a pathological event. Quite the contrary, it is a normal human experience. However, for some the stress of bereavement may lead to pathological consequences, either physical or mental.

Bereavement may place some at risk for morbidity and mortality after a loss. There have been several investigations into the morbidity and mortality effects of bereavement, especially conjugal bereavement. The findings are mixed. To date, the evidence suggests that there may be a higher risk for mortality among men, especially those older than 75 years of age, but not among women. Remarriage seems to reduce the risk for men, but the reasons for this are not clear. It may be that only the fittest of men remarry (2). The first year after the death of a spouse seems to be the time when men are most at risk. Also during the first year of bereavement there is an increased risk of suicide, especially among older widowers and single men who lose their mothers.

The evidence for increased incidents of morbidity in the bereaved presents a mixed picture. Additional studies need to be done. It is clear, however, that there is a substantial increase in the use of alcohol, tobacco, tranquilizers, and hypnotics among the bereaved, both men and women. Investigators have looked at the stress of bereavement on various immune functions in an attempt to find such a relationship (3,4 and 5). These studies may help clarify possible relationships between some bereavement and morbidity.

In addition to issues of morbidity and mortality, there is the problem of complicated bereavement. Although most people make an adequate adjustment to bereavement, the adjustment becomes complicated in some, and they develop abnormal patterns of grief (6). Among the types of complicated bereavement are the following:

1. *Chronic grief* does not seem to end, and several years later the mourner has a sense of being stuck in the process. Although there is no timetable for mourning, it is the subjective sense of “stuckness” for the mourner that helps identify this phenomenon.
2. *Delayed grief* appears at the time of a later loss but is clearly linked to an earlier loss that was insufficiently mourned. Frequently this mourning is interrupted because the loss is negated or seems overwhelming to the person, or the grieving behavior is not socially supported by others in the mourner's life.
3. *Exaggerated grief* is present when a normal grief response is exaggerated to the point where the person becomes dysfunctional. For example, it is normal to experience dysphoria after a loss, but if this affect is exaggerated to the level of clinical depression, it becomes a type of exaggerated grief. Likewise, it is normal to feel anxious after a loss. If the anxiety rises to a clinical level, such as panic attacks, phobias, or another major anxiety disorder, this would also qualify as an exaggerated grief reaction. Dysfunctional experiences that arise in the course of bereavement often receive a *Diagnostic and Statistical Manual of Mental Disorders-IV* diagnosis. Frequently, however, there has not been a previous episode of the disorder, the patient sees a relationship of his or her affect and behavior to the loss, and the patient may never again experience such a disorder after treatment.
4. *Masked grief* is the fourth type of complicated bereavement. Grief that was absent at the time of the loss appears later under the guise of a psychiatric or medical symptom. When the unmourned loss is grieved, then the symptoms usually abate. Unlike exaggerated grief, wherein the mourner sees a relationship of the symptom to the loss, in masked grief the mourner does not see such a relationship.

TASKS OF MOURNING

The clinician who is interested in working with the bereaved needs to understand the process of mourning. Mourning does not involve clear-cut stages but rather certain tasks that need to be accomplished (6). These tasks (outlined in Table 59-1) do not require a specific ordering, but if they are not accomplished, the bereaved has not made a satisfactory adaptation to the loss.

To accept the reality of the loss
To experience the pain of the loss
To adjust to the environment in which the deceased is missing
External adjustments
Internal adjustments
Spiritual adjustments
To find a way to remember the deceased while moving forward with life

From Worden JW. *Grief counseling and grief therapy*. 3rd ed. New York: Springer, 2002, with permission.

TABLE 59-1. TASKS OF MOURNING

The first task of mourning is *to accept the reality of the loss*. Even in the case of an expected death from cancer, when the family may have observed the declining physical condition of the patient, there is a certain sense of unreality when the news comes that the person has died. This sense of unreality is heightened many times over when the death is sudden or violent. After a death, many survivors experience searching behavior, looking for the lost loved one, or they may misidentify people on the street and have to remind themselves that the person is dead and will not return, at least in this life.

Disbelief that the person is dead can range from a simple hope that one will wake up from a bad dream and that this couldn't be happening to a full-blown delusion that the person is not dead. Illustrating the middle of this continuum of disbelief is the mother whose daughter was killed in a house fire. Although she visited the cemetery every day to put flowers on her daughter's grave, she went around the house saying, “I won't have you dead; I won't have you dead.” This went on for 2 years until she was helped to acknowledge the reality of the loss—that her daughter was not coming back—as well as her own need to let her go and say goodbye to her.

Another form of thwarting this first task of mourning is an effort at “mummification,” i.e., keeping the room, clothes, and other belongings of the deceased undisturbed with the hope that one day the loved one may return. For most, the searching behavior and hope for reunion are short-lived, and people accept the reality that the

person is gone and will never again return as they once were.

The second task of mourning is *to experience the pain of the loss*. Most people do not like pain and attempt to cut short the pain of grief. Others around the mourner who are not comfortable with the pain may also try to thwart the task of experiencing the pain. Nevertheless, if the pain is not felt now it may return later, associated with another loss; alternatively, it may manifest itself as some kind of physical symptom or some form of aberrant behavior.

The negation of this second task of working through the pain is not to feel. People can short-circuit this task in any number of ways. Some try to stop their feelings and deny that the pain is present through substance abuse, removing reminders of the deceased, or moving to a different location. Others idealize the dead and only allow themselves pleasant feelings. Still others cut the pain by minimizing the relationship to the deceased: “He was not very important to me.” Moving after a death may be a way to cure the pain geographically. British psychiatrist John Bowlby has said, “Sooner or later, some of those who avoid all conscious grieving break down—usually with some form of depression” (7). One of the aims of grief counseling is to facilitate this difficult second task so people don't carry the pain with them throughout their lives.

Adjusting to an environment where the deceased is missing is the third task of mourning. Adjusting to the loss means different things to different people, depending on their relationship with the deceased and the various roles the deceased played. Widows and widowers may take time to realize all that they have lost when a spouse dies: friend, lover, bill-payer, gardener, bed-warmer, etc. The awareness of all that one has lost takes time, and this contributes to bereavement being a lengthy process. Six months after the death of her husband, one widow said, “If you had asked me before he died who was the social director in our family, I would have said we both were. Now I realize that he was the one who planned the weekend events and made the arrangements.” This was not the biggest loss she had sustained, but it illustrates how awareness of losses continues to come to the fore months after a death. Some survivors resent having to develop new skills after a death and thwart this third task by not adapting to the loss. They withdraw from the world, assume a helpless posture, and refuse to face up to environmental requirements. They are held in a state of suspended growth in which they are prisoners to a dilemma they cannot solve (7).

Adjustments can be categorized as external, internal, or spiritual. External adjustments refer to the more obvious changes such as living in an empty house, taking on the role of a single parent, learning to drive, and paying bills. Internal adjustments deal with changes in one's sense of self. Bereavement can lead to intense regression wherein the bereaved perceive themselves as inadequate, helpless, or otherwise incapable of functioning. Along with this may come the sense of being unlovable. Bereavement not only means the loss of a significant other but can also mean the loss of a sense of self, in which one's self-esteem and selfefficacy are severely challenged. In a 7-year study of widowed persons, Lieberman found that one-third of widows experienced some growth after the death and that this often included a revision of their self-image. Such persons tended to be those who felt that their own self was submerged in the marriage and who found a sense of liberation after the death (8).

Spiritual adjustment has to do with one's sense of the world and how the death has challenged one's fundamental life values and philosophical beliefs—beliefs that are influenced by families, peers, education, and religion as well as life experiences. Sudden and violent deaths frequently call for these adjustments as they challenge one's sense of God, the predictability of the universe, and why bad things often happen to good people (9).

The fourth task of mourning involves *finding a place in one's life for the deceased so that one can remember and appropriately memorialize the person, yet relocating that person so that one can move forward with one's life*. If a person tries to keep the relationship with the deceased just as it was before the death, the person may become stuck and not move forward with his or her life without the deceased, closing him- or herself off from new relationships and activities. A survivor's readiness to enter new relationships depends not on “giving up” the dead spouse but on finding a suitable place for the spouse in the psychological life of the bereaved—a place that is important but that leaves room for others (10). This task also applies to bereaved parents. A mother whose daughter was killed in a tragic accident was focused for months on that event and on her loss. It was her first thought on awakening every day. Then one day she was surprised when her daughter did not occupy her first waking thought. She then realized that her daughter was dead and was never coming back, even though she desperately wanted her to. She also realized that she was alive and needed to move forward with her life. Finding a way to remember the deceased while moving forward with life is the focus of this fourth task of mourning.

This task approach to mourning can be very useful to the clinician. First, it provides the clinician with an understanding of the process and supplies a focus for the types of intervention that may facilitate the process. Second, it offers a way to understand what is happening in the case of complicated bereavement—where and how a person is stuck, and ways to develop grief therapy strategies. Third, it offers the caregiver something to do for the bereaved that can help reduce the feelings of helplessness stimulated when the mourner wants from us the one thing we cannot give—namely, the dead person back.

MEDIATORS OF THE GRIEF RESPONSE

Although all persons who have sustained a loss by death need to accomplish the tasks of mourning, a wide range of behavior can be classified as normal grief. Not all people grieve the same way any more than all people die the same way. For some, grief is strong and overpowering; for others, it is a very mild experience. For some, grief begins on hearing of a death; for others, it takes longer to begin to grieve. For some, grief is a very brief experience; for others, it goes on and on and never seems to come to an end.

It is important for the clinician to understand that grief, the personal experience of loss, is a multidetermined phenomenon. No single mediator, such as type of death (sudden versus expected), can explain the variations in experience. An understanding of these mediators can be useful to the clinician who is trying to identify in advance how someone might grieve to offer preventive mental health intervention to those most likely to adapt poorly to the loss. Table 59-2 contains what seem to be the most important mediators of a grief response (6).

Nature of attachment
Mode of death
Historical antecedents
Personality variables
Social factors
Changes and concurrent stressors

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TABLE 59-2. MEDIATORS OF A GRIEF RESPONSE

The first mediator of a grief response is the *nature of the attachment*. The most intense and often most difficult grief responses occur (a) when the attachment between the bereaved and the deceased was very strong, (b) when the deceased was needed to support the survivor's sense of selfworth and self-esteem, (c) when the survivor was highly dependent on the deceased, or (d) when the relationship was a highly ambivalent one.

The *mode of death* can and does influence the grief response. A sudden death may be more difficult to grieve than one with advance warning. The natural death of an older person may be easier to grieve than the accidental death of a young child or the suicidal death of a teenager. Geographical distance at the time of death, multiple losses, and uncertain losses can all increase the probability of a poor outcome.

Historical antecedents are also important. How one handled previous losses and how well they were resolved can play a role in current loss. Also, a history of clinical depression may portend a more difficult mourning period.

Personality variables, such as age, gender, tolerance for pain and anxiety, personality structure, and ability to express feelings, also contribute to variations in grieving.

Social factors constitute another mediator of a grief response. Each person belongs to various social subcultures, such as ethnic and religious groups, which provide guidelines and rituals for grieving behavior. Social support is also an important factor in mourning. Those who feel supported by family and friends find it easier to grieve than those who do not or those whose social environment actively suppresses the expression of grief.

A final mediator is the *number of changes and concurrent stressors* experienced by the family as the result of the death. In the Harvard Child Bereavement Study of

bereaved families who had lost a parent to death, the strongest predictor of both the depression of the surviving parent and the functioning of the school-age children was the number of changes that the family experienced as the result of the death (11). Families who experience fewer concurrent stressors as a result of the death do better than families for whom stressors are many. Closely related to these family stressors are the family coping styles. Families who could engage in more active coping and who could redefine and reframe problems were less affected by these concurrent stresses than families that could not do this.

INTERVENTION PRINCIPLES

Given the tasks of mourning and the mediators of grief, there are certain implications for a comprehensive program of palliative care through which the bereaved can be helped (Table 59-3).

Facilitate anticipatory grieving
Before death, encourage communication between patient and family
At the time of death, encourage and provide for family presence
After death, encourage reminiscing
Help people deal with all of their feelings
Normalize grief behaviors
Identify complicated bereavement and make referrals to a professional for grief therapy
Be aware of the special features of the bereavement over the loss of a child

TABLE 59-3. INTERVENTION PRINCIPLES

First, recognize that both the dying patient and the family can and do grieve before a death. Being aware of this and helping the patient and family to understand this can help them to cope with the alienation that can occur when someone is dying.

Second, encourage families of the dying to say those things to each other that need to be said before the death. This can leave the survivor with less unfinished business to be dealt with after the death. Family members often need permission from the caregiver to do this. A sentence or two can go a long way to help the family members do what they inwardly want to do but may feel awkward doing.

Third, allow the family to be with the person as he or she is dying, and allow them to be with the body after the death. This can be very salutary in facilitating the first task of mourning—making the death real. There is nothing like the confrontation with the loved one's body to bring home the reality of the loss. A program that encourages this and makes provision for it can make an important contribution to bereavement.

Fourth, after the death, encourage conversations about the deceased. Nothing works better to bring home the reality of the loss than verbalizing about the deceased. The problem is that many families cut short this process because they don't want to hear about something they already know. An enlightened caregiver can encourage those who want and need to talk to do so. The mourner must first believe that the death happened before he or she can deal with the feelings that go with such a loss.

Fifth, help people deal with their feelings. Most do not have difficulty with sadness, but many do have difficulty with the anger, guilt, and anxiety that may follow a loss. Helping them to understand that a wide range of these feelings is normal and to find appropriate outlets for these feelings is all part of a comprehensive program of bereavement care.

Sixth, know what normal grief behavior is, and offer reassurance if family members are having experiences they have never had before and feel that they are going crazy. In our research and clinical experience we find that people seldom decompensate and go insane after a loss, but they may feel they are going crazy because of the unfamiliarity of these experiences. If the clinician knows that hallucinations, distractedness, nocturnal orgasms, sleep disturbance, appetite loss, and other anomalous experiences are normal, the appropriate reassurance can be given.

Seventh, the clinician should also know the signs of a complicated bereavement, and if these occur, should make a referral to a professional for grief therapy. The list of these signs and symptoms is too long for this report but can be found in detail in other places (6,12).

Eighth, know that pediatric oncology presents its own special features. Parents who lose children are among those with the most difficult grief to bear. To lose a child is not only to lose someone out of season but also to experience special strains on the whole family system. Much has been written on this subject, and support groups are available for bereaved parents, such as those sponsored by The Compas- sionate Friends. The concerned oncologist should be familiar with these resources.

BEREAVEMENT SERVICES

There are several considerations in the establishment of bereavement services as part of a palliative care service. They include such questions as these: Who should be served? Who should do the counseling? When should counseling begin and how long should it be continued? Where should this counseling be done? Let's look at these questions one by one.

Who should be served? There are basically three philosophies of grief counseling. The first is to offer such services to everyone who is bereaved. This, however, is not a costeffective approach, and not everyone needs grief counseling. Many, if not most, do very well on their own without the need for special intervention. A second and very common philosophy is to wait and see which people get into difficulty in their mourning and to offer intervention at that point. There is nothing wrong with this approach except that it requires a person to experience a high level of distress or poor coping before intervention is offered. A third approach is to screen individuals around the time of death to predict who among them will not be doing well a year or two later. Preventive mental health counseling can be offered to those who are predicted to be at risk to preclude later negative sequelae. This type of approach makes sense when valid predictors and risk factors have been identified and there is a high level of reliability in a set of predictors. Parkes and others have identified such risk predictors for conjugal bereavement, and Worden and Silverman have developed a screening instrument for high-risk children who have lost a parent to death (13,14,11).

The question of who should be counseled raises the issue of unit of care. Who in a family should be given counseling? When a spouse has died, the surviving spouse may prefer to be seen alone without other family members. When children die, the parents may prefer to be seen together. I prefer to have at least one session with the entire nuclear family, do an assessment of need, and make intervention referrals at that point.

Who should do the counseling? There are several possibilities. One involves a trained professional, such as a social worker, nurse clinician, psychologist, chaplain, or other mental health professional. The advantage here is the obvious training and experience of such personnel. Another possibility is the use of trained volunteers to intervene with or befriend the bereaved. Sometimes these volunteers have been bereaved themselves in the past and use their own experience to try and be helpful. Many hospice programs and groups like The Compassionate Friends use this type of volunteer. A third possibility is the use of nonprofessional volunteers with professional backup. Deci- sions regarding personnel need to fit the particular organization that is offering counseling, but the emphasis clearly needs to be on trained individuals.

When should counseling begin? There is a general consensus that the best time to start is between 3 and 8 weeks after the event (13). Earlier than that, the bereaved may be very involved with family, and the reality of the loss may not have set in. After 8 weeks, some have sealed off their feelings and may be hesitant to start the process all over again. For most bereaved individuals, at 2–3 months after the death, the reality of the loss and its consequences is setting in, pain is at a high point, and support that may have been there at the time of the funeral may be waning.

How long should counseling for individuals and families continue? There is no general agreement on this point. In the United States, hospice care programs usually follow-up with family members in one way or another for a year after the death. Such follow-up may be by phone, letter, or personal visit. This 1-year time frame was informally established and is not necessarily based on research. In fact, research shows that for some bereaved, the most difficult time, with the highest possibility for developing poor adjustment, occurs in the second year of bereavement. This argues for the need of a good screening instrument to predict the individuals who are at

most risk in the second year of bereavement.

Where should counseling take place? Some bereaved are hesitant to return for help to a hospital, a hospice, or to another place where the loved one died. This is especially true in the early months after a loss. Many people feel most comfortable in their own homes, and this may be the best place to see them in the early weeks after a loss. Some bereaved prefer to talk to someone on the telephone because of the anonymity, but face-to-face contact is usually preferable so that nonverbal communication can be assessed and used in the intervention. Later on it can be useful for the bereaved person to return to the place of death as a point of reality for that loss.

Groups for bereaved individuals can be very effective in facilitating the grief process. In a well-run group, mourners can find others who have experienced similar losses and can gain support from such individuals. Knowing that they are not alone in their loss, and knowing that others in the group will not be pushing them to finish their grieving, can be helpful to most people. However, not everyone wants to attend a bereavement group; women are more frequent attenders than men. Men are more likely to attend a group whose aim is education about the grief experience or one whose aim is addressing specific problems such as how to be an effective single parent.

CONCLUSION

Bereavement is one of life's greatest stresses and an experience from which none of us can escape. The clinician who learns from his or her own experience of loss can use this understanding to fashion interventions that can be helpful to the bereaved. Knowing what was and was not helpful to us in our time of need can direct us in making interventions, both verbal and programmatic, that are healing to the families in our care.

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60

EDUCATION AND TRAINING IN PALLIATIVE CARE

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Palliative care represents a new medical discipline in the United States. Although not yet a full-fledged medical specialty or subspecialty, palliative care is rapidly emerging as a topic of focused education for physicians and other health professionals concerned with care of the dying. Many studies have documented the poor state of palliative care education and palliative care educational resources in the United States (1,2,3,4,5,6,7,8,9 and 10). There is widespread agreement that all facets of the end-of-life experience have been neglected in health professional education, including (but not limited to) pain and symptom management, communication skills, ethics, personal awareness, and hospice care. This chapter focuses on physician education within palliative care, although much of the discussion is directly applicable to other health professional disciplines. Both the terms *end of life* and *palliative care* are used in this chapter. There is consensus among palliative care professionals that the term *end of life* represents a restricted vision of the broader concept of *palliative care*. As a cultural term, *end of life* is typically used to describe the near-dying experience, usually the last few weeks of life. In contrast, *palliative care* refers to the health care issues for patients and family facing any chronic, life-limiting illness, at any point in the disease trajectory.

REQUIREMENTS FOR PALLIATIVE CARE PHYSICIAN EDUCATION IN THE UNITED STATES

Until very recently, there were no mandated requirements for palliative care physician education. Not surprisingly, studies examining how and where palliative care is taught have found that teaching is uncoordinated, often elective, and mostly in lecture format, with limited patient contact (3). Although some U.S. medical schools have developed dedicated palliative care courses or comprehensive curricula, this has been the exception (11,12,13,14,15,16 and 17). In 2000, the Liaison Committee on Medical Education (LCME), the accrediting authority for U.S. medical schools, mandated that end-of-life care be part of every school's curriculum: “Clinical instruction should cover all organ systems, and must include the important aspects of preventive, acute, chronic, continuing, rehabilitative and end of life care” (18). Although this represents a major step forward in palliative care education, specific details from LCME as to what constitutes *end of life* remains to be defined.

Graduate education requirements for palliative care training are highly variable. According to the individual residency and fellowship program requirements listed by the Accreditation Council for Graduate Medical Education in 2000, only geriatrics, family medicine, internal medicine, neurology, and hematology/oncology have substantive requirements for palliative care training, and only geriatrics specifically mandates training via a clinical experience in hospice care (19,20,21 and 22). Recently, the Accreditation Council for Graduate Medical Education adopted six “general competencies,” applicable to all graduate training programs (23). Included are two domains of interest to the palliative care educator, *interpersonal and communication skills* and *professionalism,* domains that include topics of ethics, compassion, respect, and altruism. In the realm of testing, the National Board of Medical Examiners is working to expand end-of-life content on test questions administered to medical students and interns in the United States as part of the U.S. Medical Licensing Examination (24).

Although there is no national requirement for physicians already in practice to acquire new knowledge and skills in palliative care, the American Medical Association has encouraged all its member physicians to participate in *Education for Physicians on End-of-life Care* (25). One final training requirement comes via state law. Starting in 2000, California began requiring that all applicants for a medical license “successfully complete a medical curriculum that provides instruction in pain management and end-of-life care” (26). As with the LCME requirements, the exact criteria to determine what constitutes end-of-life instruction have not been defined.

Curriculum Guides for Palliative Care Physician Education

What should be included within the educational domain of Palliative Care? In the past 10 years, several groups have worked to define the components of a comprehensive palliative care curriculum. The *Canadian Palliative Care Curriculum* was developed as a guide to undergraduate palliative care education for Canadian medical schools (27). It contains a list of attitude, knowledge, and skill objectives for 22 different domains including symptom control, ethics, psychosocial issues, home care, cost containment, and quality assurance. In Great Britain and Ireland a curriculum was developed that includes specific palliative care curriculum goals for each training year (28).

One set of teaching objectives for U.S. physicians was published in 1994 by Schonwetter and Robinson (29). In 1998, a national consensus conference on U.S. undergraduate and graduate education was held, outlining curriculum features and opportunities for education across different educational venues (30). The outcome of this conference was a series of position papers outlining idealized curriculum and training opportunities (31,32,33 and 34). Although each of these discusses a somewhat different aspect of endof-life care education, there is broad similarity on the major educational domains (Table 60-1). Another consensus document was developed by participants from 11 U.S. medical schools participating in a medical school curriculum project sponsored by *Choice-in-Dying* with funding from the Greenwall Foundation. This document outlines goals and objectives for medical student education along with a discussion of potential student assessment measures and curriculum implementation strategies (35).

Educational domains
Pain assessment and treatment
Non-pain symptom assessment and treatment
Ethical principles and legal aspects of end-of-life care
Communication skills, personal reflection
Psychosocial aspects of death and dying
Death as a life-cycle event
Psychological aspects of care for patient/family
Cultural and spiritual aspects of end-of-life patient care
Suffering/hope
Patient/family counseling skills
Working as part of an interdisciplinary team
Care settings in which training should occur
Hospital
Palliative care consultation service or inpatient unit
Outpatient clinic
Home and home hospice
Residential hospice
Long-term care facility

TABLE 60-1. DOMAINS AND LOCATIONS FOR PALLIATIVE CARE PHYSICIAN EDUCATION

Curricula have been promoted for specific domains within palliative care. The American Association for Cancer Education published cancer pain management learning objectives for medical students and primary care residents (36). The American Society of Clinical Oncology published similar cancer pain objectives for medical oncology training and continuing education programs (37). Broad communication skills learning objectives (including objectives for end-of-life care) for medical students in the United States have been written by the Association of American Medical Colleges as part of its Medical School Objectives Project (38). More detailed objectives were compiled at the Medical College of Wisconsin in 1998 as part of an effort to outline specific communication skills objectives that should be mastered within each

year of medical school training (39).

For graduate education, the American College of Physicians and American Academy of Family Physicians have published curriculum guides for the care of the dying (20,22). For physicians already in practice, the American Academy of Hospice and Palliative Medicine developed a curriculum designed for “medical educators and practicing physicians” (40). This curriculum includes 22 modules, each containing a listing of learning objectives and core content for key domains in symptom control, communication, hospice care, and ethics. The American Academy of Hospice and Palliative Medicine curriculum was originally designed for physicians working as hospice medical directors, but can easily be adapted for other levels of physician education. The *Education for Physicians on End-of-life Care* project, designed for physicians in practice, contains a comprehensive palliative care curriculum including pain and symptom control, communication skills, ethics, and legal aspects of care (25). Again, this curriculum can be easily adapted for all levels of physician training. The newest comprehensive curriculum, developed in 2001 for medical oncologists and oncology trainees by the American Society of Clinical Oncology, includes 29 modules covering symptom control, communication skills, and related aspects of palliative care. Curriculum standards for palliative care fellowships are currently under development under the aegis of the American Board of Hospice and Palliative Medicine and the American Academy of Hospice and Palliative Medicine. An extensive listing of peerreviewed educational tools, curriculum guides, reference articles, and links in palliative care is available at the End-of-Life Education Resource Center, www.eperc.mcw.edu (41).

PLANNING A PALLIATIVE CARE EDUCATIONAL INTERVENTION

Needs Assessment for Curriculum Development

The first step in the design of an educational intervention is the performance of a needs assessment. The purpose of a needs assessment is to understand the gap between what is currently being taught and evaluated and the ideal (42). A needs assessment is used to understand and characterize the problem that needs fixing and how the problem impacts on different stakeholders, such as students, patients, or family members. A comprehensive needs assessment should be able to identify strengths and weaknesses in the current system of education along with barriers and opportunities for change.

To accurately understand the nature and scope of the problem, information needs to be obtained, ideally from multiple different sources, using different techniques. A key first step in the process is to understand what an idealized education plan should include. This information can be obtained by reviewing the literature, seeking consensus documents that define best educational practice, and conducting interviews with experts and colleagues who have undertaken a similar task (42). The next step is to obtain local data to understand how your current program is or is not achieving the best practice standards. Although abundant national data may be available, it is local data that are most useful in convincing change agents of the need for action. Data that can be rather easily obtained include surveys of attitudes, self-confidence, or knowledge of stakeholders; informal meetings soliciting information about current and desired curriculum and evaluation methods; and chart reviews (42,43). More sophisticated and laborintensive methods include formal focus groups, skills-based assessment (see the section Assessment of Learner Performance and Program Evaluation), and direct observation of clinical practice. The final step in the needs assessment process is to synthesize the information, prepare a report, and present the information to key stakeholders, individuals such as program directors or curriculum deans who can assist in making change happen.

Different multidimensional palliative care needs assessments have been reported for different populations of learners. The Palliative Care Education Assessment Tool (PEAT) is a comprehensive “curricular mapping” tool, developed as a self-assessment tool to be used by medical schools (44). PEAT is used to assess curriculum across seven domains: palliative medicine, pain, neuropsychologic symptoms, other symptoms, ethics and law, patient/family/caregiver nonclinical perspectives on end-of-life care, and clinical communication skills. The successful application of PEAT, as a method to obtain needs assessment data and plan for curriculum reform, has been demonstrated in a cohort of New York medical schools (44).

Ury et al. reported their experience with a needs assessment process developed for one internal medicine residency (45). This process included distribution of a survey, focus groups, and topic rankings. Weissman et al. described a complex needs assessment process for understanding end-of-life education in a cohort of more than 150 internal medicine residency programs (43,46,47 and 48). This process includes (a) completion by the residency program director of a baseline assessment identifying their program's demographic characteristics, teaching content and methods, resident assessment methods, and perceived barriers and resources for end-of-life care and curriculum reform; (b) a separate but identical survey to be completed by a chief resident to assess for perceived differences in educational offerings between faculty and residents; and (c) surveys of self-confidence, concerns, and knowledge surrounding end-of-life care. Other focused assessment instruments have been described to assess attitudes and knowledge in various domains of end-of-life care (49,50,51 and 52).

Teaching Methods in Palliative Care Education

Teaching and learning are not the same; teaching is what the educator does, learning is what the learner acquires from the educational experience. The educators' attitudes, knowledge of the subject matter, skills, *and* educational techniques directly influence the relation between teaching and learning. Key to the success of a palliative care educational encounter is awareness of the key principles of adult learning. These include keeping the experience *learner-centered*, with relevant information keyed to the learners' *need to know,* and understanding that adult learners make choices about their participation (e.g., they leave the room if the information is not relevant to their needs). One way to obtain buyin from an audience of adult learners is to ask at the start of a teaching session, “Why are you here today? What do you hope to learn from this encounter?” Responses can be written on a flip chart or overhead projector, with the remainder of the education geared around the responses. Another suggestion is to start with a brief exercise that helps build a sense of *tension* for learning: Begin a teaching session by asking the learners two to three shortanswer or multiple-choice questions, holding back the answers until late in the teaching session.

Table 60-2 details possible teaching methods for palliative care education, sorted by the type of desired learning objective. Delineating learning objectives is the first key step in planning any educational experience. Objectives communicate to the learner what is expected of the educational encounter and form the basis for evaluating the impact of training. Objectives are divided into one of three broad categories: Attitude objectives are concerned with values and emotions, knowledge objectives relate to acquisition of facts, and skill objectives relate to performance of a specific activity. Objectives should contain four discrete items: the *audience*, the *desired behavior*, the *condition* under which the behavior will be learned, and the *degree* to which the new learning will be demonstrated (53).

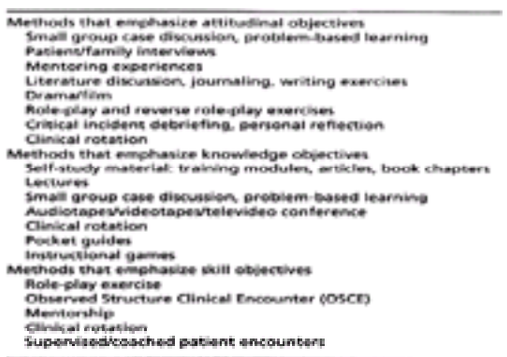
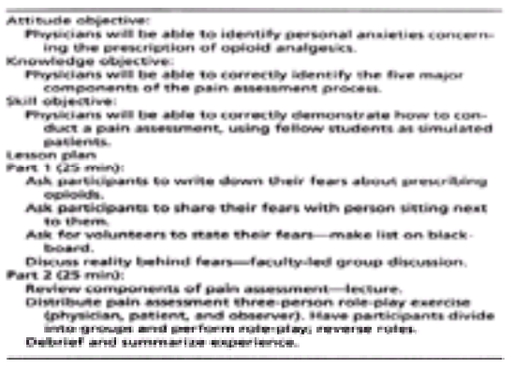

Methods that emphasize attitudinal objectives
Small group case discussion, problem-based learning
Patient/family interviews
Mentoring experiences
Literature discussion, journaling, writing exercises
Drama/film
Role-play and reverse role-play exercises
Critical incident debriefing, personal reflection
Clinical rotation
Methods that emphasize knowledge objectives
Self-study material: training modules, articles, book chapters
Lectures
Small group case discussion, problem-based learning
Audiotapes/videotapes/televideo conference
Clinical rotation
Pocket guides
Instructional games
Methods that emphasize skill objectives
Role-play exercise
Observed Structure Clinical Encounter (OSCE)
Mentorship
Clinical rotation
Supervised/coached patient encounters

TABLE 60-2. EDUCATIONAL METHODS FOR PALLIATIVE CARE EDUCATION

Given the pervasive and often negative attitudes that shape caring for the dying, it is advisable to include a mixture of attitude, knowledge, and skill objectives in all training experiences. Thus, it is also desirable to include a mixture of teaching methods in any one educational experience. Table 60-3 details an example of a 1-hour pain management teaching session that includes diverse teaching methods, including personal reflection, group discussion, lecture, and role-playing.



Attitude objective:
Physicians will be able to identify personal anxieties concerning the prescription of opioid analgesics.
Knowledge objective:
Physicians will be able to correctly identify the five major components of the pain assessment process.
Skill objective:
Physicians will be able to correctly demonstrate how to conduct a pain assessment, using fellow students as simulated patients.
Lesson plan
Part 1 (25 min):
Ask participants to write down their fears about prescribing opioids.
Ask participants to share their fears with person sitting next to them.
Ask for volunteers to state their fears—make list on blackboard.
Discuss reality behind fears—faculty-led group discussion.
Part 2 (25 min):
Review components of pain assessment—lecture.
Distribute pain assessment three-person role-play exercise (physician, patient, and observer). Have participants divide into groups and perform roleplay; reverse roles.
Debrief and summarize experience.

TABLE 60-3. SAMPLE OBJECTIVES AND LESSON PLAN FOR 50-MINUTE TEACHING EXERCISE ON PAIN ASSESSMENT FOR PHYSICIANS

In general, addressing attitudes is the most challenging feature of palliative care education. It is a truism of medical education that attitudes cannot be taught. Rather, a shift in attitudes requires that the learner feel safe and respected and be ready to give up one attitude (e.g., “I am afraid to use opioids for fear of causing addiction”) for another (e.g., “opioids rarely lead to addiction, are safe, and improve quality of life”). General principles of discussing attitudes are listed in Table 60-4.

How do attitudes form?
Imitation of others: positive and negative.
Direct instruction.
Observation of rewards and punishments.
Pressure to conform.
Cognitive dissonance: facts inconsistent with belief.
How do attitudes change?
Recognize that attitudes involve ego-involvement.
Shared group attitudes are more resistant to change.
There must be a willingness to change.
Individuals must be ready to change.
Exhortation, information, and rational argument have a limited role in the learning or changing of attitudes.
Effective teaching capitalizes on “teachable moments,” in which the learner is emotionally or intellectually aroused by a question, contradiction, or problem.
Attitudinal development is fostered in situations in which the learner can be active and can engage with others around real problems.
Attitudes are best learned/changed when:
The learner is able to examine personal feelings/attitudes in an open and nonthreatening dialogue with peers, and concrete knowledge and skills are taught that relate to the desired attitudes.
The learner has an opportunity to practice the new behavior, thus making a commitment.
The learner has the opportunity to reflect on the meaning, difficulties, and rewards of attitudinal change.
Role-playing and role-reversal encourages the learner to take an alternative perspective and may foster an empathic awareness of the other's experience.
Role models and mentors are crucial to the process of learning attitudes, especially when the learner is making a transition.
Feedback about the learner's progress toward explicitly desired attitudinal objectives can help promote self-reflection and self-learning.

Provided by Susan Block, M.D., with assistance from Lynn Wilkerson, Ed.D.

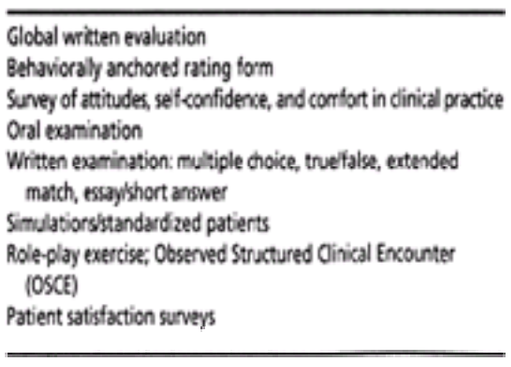
TABLE 60-4. TEACHING ATTITUDES

Knowledge objectives are the easiest to teach; perhaps that is why the traditional 50-minute lecture remains the most commonly used educational format in medical education. However, other modalities do exist, notably self-study guides, journal articles, video-and audiotapes, and use of games (e.g., *Medical Jeopardy*).

Teaching directed at skill objectives requires the learner to practice and demonstrate a defined skill such as patient counseling, calculating equianalgesic doses, or death pronouncement. Teaching sessions based on skill objectives requires preparation of case studies or role-playing scenarios, training simulated patients, or selecting and briefing real patients to be used in a training setting.

Assessment of Learner Performance and Program Evaluation

Table 60-5 lists commonly used assessment methods in palliative care. As with teaching methods, different assessment methods work best when appropriately matched to the learning objective. Attitudes are best assessed through personal interactions, directed questioning, and surveys. Knowledge can be assessed via oral or written examinations, and skills through direct observation or written problem solving (e.g., calculating opioid equianalgesic doses). Assessment techniques can also serve as a teaching tool. For example, asking physicians to take a multiple-choice examination and then reviewing the answers combines both learning and assessment. Another common example is to have learners practice communication skills with a simulated patient, who then gives immediate feedback to the learner.



Global written evaluation
Behaviorally anchored rating form
Survey of attitudes, self-confidence, and comfort in clinical practice
Oral examination
Written examination: multiple choice, true/false, extended match, essay/short answer
Simulations/standardized patients
Role-play exercise; Observed Structured Clinical Encounter (OSCE)
Patient satisfaction surveys

TABLE 60-5. LEARNER ASSESSMENT METHODS

Evaluating the impact of a teaching experience can be done at several different levels, depending on the desired information. At the most basic, learners can be assessed using a “happiness survey,” i.e., questions about the global quality of teaching, whether the learning objectives were met, the teaching skills of the educator, the quality of audiovisual material, etc. The next order of evaluation is to understand if learning occurred. Administering a series of questions using a prepost test design is a commonly used method of assessing the immediate impact of an educational experience. Unless a different set of questions is used in the post test, however, there is danger of test retest bias. Delayed post tests can be administered weeks, months, or years after a specific learning experience, to assess retention of information across time. However, interpretation of this data is fraught with hazard, as intercurrent learning activities distort the impact of the original teaching.

A different form of post test survey, the retrospective pre-post test, asks learners to rate their *change* in attitudes, knowledge, and skill at the conclusion of an educational program, compared to the beginning of the program (54,55 and 56). This is a very effective evaluation tool in palliative care, because it is common for physicians to think that they already know the facts of a given topic at the start of the teaching program, when in fact they only become aware of their deficiencies during the presentation.

The highest order of evaluation works to assess the impact of an educational experience on physician behavior and patient care (e.g., reviewing charts for written documentation of pain assessment information before and after a learning exercise on pain assessment). Other examples include chart audits for analgesic prescribing, videotaping patient encounters to assess communication skills, or asking patients to complete a survey rating their physician's communication skills.

EDUCATIONAL ISSUES IN SPECIFIC PALLIATIVE CARE DOMAINS

Pain Education

Pain must be controlled before physicians can assist patients with the myriad of physical, psychological, and spiritual problems at the end of life. Yet physicians frequently fail to apply currently accepted standards of care for acute or chronic pain management. Moreover, it is clear that despite a multitude of clinical guidelines, position papers, workshops, lectures, grand rounds, journal articles, and book chapters written about pain management, clinical practice is still far from optimal

(57,58,59 and 60).

The primary reason that conventional education formats fail to translate into a change in clinical practice is that physicians harbor a host of attitudes about pain and pain management that inhibit the appropriate application of knowledge and skills. These attitudes can be divided into two broad categories (57). First are physicians' attitudes about pain, which reflect societal views about the meaning of pain and pain treatment (61). A second category of negative attitudes relates to fears and myths about opioid analgesics: fears of addiction, respiratory depression, and regulatory scrutiny, along with the secondary consequences of these fears—malpractice claims, professional sanctions, loss of practice privileges, and personal guilt about potential culpability for causing death (62,63 and 64).

In addition to attitudes, deficits in pain knowledge and skills are widespread. Physicians generally do not know the clinical pharmacology of opioid and nonopioid analgesics, how to conduct a pain assessment, or how to use nondrug analgesic treatments (e.g., antineoplastic, anesthetic, and behavioral), and they lack skills in patient education and counseling regarding pain and pain treatment. Educational techniques and results from various pain education programs have been reported and reviewed extensively (59,60,65,66,67,68,69,70,71 and 72). Key findings include the following:

- Pain education must include attention to attitudinal issues along with knowledge and skills.
- Pain education must be longitudinal, not just part of a pharmacology course in the preclinical years.
- Pain education of physicians, together with nurses and pharmacists, can lead to significant empowerment and local change in practice.
- To most effectively impact pain management practice, education should be coupled to other elements of institutional change such as quality monitoring, development of routine assessment and documentation procedures, and standards development.

Ethics, Law, and Communication Skills Education

The specific content areas in ethics and communication skills necessary for palliative care education are listed in Table 60-6. There is considerable content overlap between ethics and communication skills. For example, to care for patients effectively, trainees need to understand the ethical and legal framework of advance directives *and* have the communication skills necessary to discuss these with patients. Similarly, trainees need to understand the ethical and legal background to make decisions about treatment withdrawal *and* to acquire the skills to discuss these issues with patients and families.

Ethics/law
Informed consent
Decision-making capacity
Advance directives, surrogate decision makers
"Do Not Resuscitate" orders
Treatment limitation and withdrawal
Medical futility
Assisted suicide and euthanasia
Cross-cultural care
Truth-telling
Communication skills
Empathic listening
Discussing advance care planning
Giving bad and sad news
Running a family conference
Discussing treatment goals
Discussing treatment limitation or withdrawal
Discussing hospice referral
Death pronouncement
Discussing autopsy and organ donation
After-death care/bereavement call/card

TABLE 60-6. ETHICS/LAW AND COMMUNICATION SKILLS DOMAINS

There is a rich literature on educational methods and outcomes in ethics and communication skills education (73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114 and 115). Although ethics is generally considered a preclinical course in medical school, it is advisable that training in ethics be incorporated throughout medical school, residency, and fellowship training. As the level of professional responsibility increases with each year of training, such responsibility imposes demands on the trainee to make increasingly complex and ethically challenging decisions. Such decisions often strain the trainees' personal understanding of professionalism and altruism and thus merit dedicated time for self-reflection and mentorship. Educational methods particularly suited to ethics instruction include case studies, small group discussion, mentorship, and narrative education. This is not to suggest that a lecture on the legal aspects of informed consent is not a valid educational tool, only that most ethical issues require active discussion and reflection to be incorporated into one's system of medical decision making.

For many communication topics, prior knowledge of the relevant ethical/legal framework is necessary before actually practicing the skill. Educational methods specific to communication skills training include demonstration and mentoring, role-playing, use of simulated patients, observed structured clinical encounter, and direct observation of clinical encounters. In addition, personal reflection and discussion, before and after patient encounters, is critical to allow the trainee an opportunity to debrief what are typically emotionally laden discussions.

Clinical Training Experiences

In the past 10 years, there has been increasing interest in developing clinical training experiences in hospice and palliative care. Hospital-based palliative care teams are thought to be a valuable venue for clinical education in palliative and end-of-life care (116,117 and 118). Trainees can learn how to work within a multidisciplinary group and can experience a truly collaborative process with the educational focus enlarged to include the physical, psychological, social, and spiritual dimensions of care. Two reports, one involving family practice residents and one involving hematology/ oncology fellows, have documented improvements in palliative care knowledge, comfort, and selected skills through a clinical palliative care rotation (119,120). The durability of the educational impact of these experiences on trainees has not been examined.

Clinical rotations that involve home or residential hospice experiences have been reported by several medical schools (13,14,15 and 16,121,122,123,124,125 and 126). The University of Maryland and the University of North Dakota School of Medicine and Health Sciences provide examples of clinical hospice experiences. In the junior year, Maryland students rotate through hospice sites for 1 half-day per week during the month-long ambulatory care block, receiving didactic instruction and reading and writing assignments, and participating as members of the multidisciplinary team in the care of three to six hospice patients (15,16). Students who were assigned this course scored 20% higher (p <.001) on a 60-item palliative medicine written examination than fellow classmates who did not. At the University of North Dakota, a 5-day hospice experience for junior students has been offered since 1995. Students engage in a combination of didactic presentations, home visits, interdisciplinary rounds, and personal journals (13). Significant pre-post test changes in attitudes were demonstrated.

Few reports of clinical end-of-life training experiences for interns and residents exist (127,128 and 129). Stanford University Medical School piloted a mandatory 4-week hospice and nursing home rotation for interns (128). Clinical time is spent caring for hospice and nursing home patients. At the end of the rotation, interns noted significant changes in their attitudes and knowledge about end-of-life care. Liao has reported early experience with a year-long, elective home hospice experience for third-year internal medicine residents (129). Residents reported improved comfort and self-confidence in dealing with end-of-life issues.

Hospice/palliative care rotations can have sustained effects. In one study, physicians who elected a 2-week clinical and didactic hospice/palliative care rotation during their fourth year of medical school completed a questionnaire 2–5 years after graduation. On a scale of 0–4, they gave the course a “4” on “how it affected my current communication with patients and knowledge of pain control”; 73% said it rated a “4” on understanding of quality-of-life issues in their current practice (126). The physicians also volunteered that the course improved their ability to help patients make decisions, and improved their knowledge and attitudes toward dying patients and the effect of disease on families.

Personal Awareness Training

Practitioners of palliative medicine and all clinicians who care for dying patients are likely to benefit from increased personal awareness of themselves, both as clinicians and as teachers (130,131). They are unlikely, however, to have received training in how to deal with the emotions that arise when caring for patients with progressive disease or with the dying patient. Physicians who do not receive such training may rely on detachment, and may not engage in the kinds of relationships that make practice feel worthwhile and that prevent burnout (132,133 and 134). These physicians are more likely to distance themselves by ignoring or paying selective attention to the cues patients offer that suggest they would like to talk about underlying concerns, trivializing those concerns by giving premature or false reassurance, or simply by changing the topic (134). Previous personal experiences with dying friends or relatives, lack of understanding of the impact of losses in their own lives and failure to grieve those losses, and lack of personal role models for how to cope effectively with emotional pain leave students and practitioners unprepared for the challenges such patients present. Without knowing why, physicians may find themselves either overinvolved or distant from terminally ill patients, and may feel a need

to continue to provide aggressive, cure-oriented care, long past the point of benefit to the patient.

Undergraduate course, residency, and fellowship directors have a number of options that can help trainees. A recommended curriculum to increase personal awareness of residents has been described (131). Settings for personal awareness training can include support groups, Balint groups, family of origin group discussions, meaningful experiences discussion, personal awareness groups, literature in medicine discussion groups, and psychosocial morbidity and mortality conferences (135).

As part of personal awareness education, students and trainees should examine their own death anxiety ("the fear of extinction, annihilation, obliteration, or ceasing to be").Trainees with significant death anxiety, who suffer stress from uncertainty, who are reluctant to disclose uncertainty, or who are anxious about attachment to patients, are more likely to have negative attitudes toward dying patients (136). Both death anxiety and uncertainty can be addressed in medical student curricula. The one controlled longitudinal study on this topic involved 99 medical students who participated in a course designed "to study the ethical, emotional, and cultural aspects of death and dying" (137). Students who took the course had significantly more positive attitudes immediately after completing the course and maintained them through their fourth year of school.

PALLIATIVE MEDICINE FELLOWSHIPS

Palliative medicine training is needed to prepare medical trainees for community or academic careers. Neither the knowledge and skills, nor the exposure to working with interdisciplinary teams needed for such a career, are found in any existing residency or fellowship training programs. As of April 2001, there were 18 U.S. programs offering physician fellowships in palliative care (138). In addition, starting in 2001, the Department of Veterans' Affairs will be providing support for physician fellowships in a limited number of training sites. Literature on the curricula and outcomes of current U.S. palliative care fellowships is scant (139,140 and 141). A consensus panel composed of the directors of the palliative care fellowships along with representatives from the National Hospice and Palliative Care Organization, the American Academy of Hospice and Palliative Medicine, the American Board of Hospice and Palliative Medicine, and the Department of Veterans' Affairs, is currently working on a document to define a core curriculum for palliative medicine fellowships.

FACULTY DEVELOPMENT

Faculty development is needed if goals in undergraduate and graduate palliative care education are to be met. A comprehensive faculty development program should include elements of professional, instructional, leadership, and organizational development (142). Several courses, typically multidisciplinary in design, have been developed in the United States, with the explicit goal of training academic faculty to become role models for palliative care education. *The Program in Palliative Care Education and Practice* at Harvard University includes didactic and experiential exercises in communication, pain and symptom management, ethics, cultural implications, teaching and learning styles, educational techniques, religious and spiritual concerns, personal awareness, organizational change, and grief and bereavement (138). Learners attend two 7-day intensive sessions, separated by 7 months, during which they work on projects at their home sites and continue education through casestudies discussed via email. The *Palliative Care Role Model program* is a 40-hour course given over 9 months, with physician, nurse, social worker, and physical therapist faculty from the Massachusetts General Hospital, Brigham and Women's Hospital, Dana-Farber Cancer Institute, and Harvard Pilgrim Health Care. The Mentorship program, sponsored by the *Network Project* at Memorial Sloan-Kettering Cancer Center is "an interdisciplinary, multimodality training program" that includes a 2-week observership in cancer pain management, psychosocial oncology, and cancer rehabilitation (143).

At the Medical College of Wisconsin, Weissman reported results of an 8-week, 12-hour faculty development program for academic physicians (56). Significant improvement in end-of-life knowledge and self-confidence and education skills was noted. A 1-week clinical experience for physicians, nurses, pharmacists, social workers, and chaplains has been offered at Northwestern University Hospital since 1995. Evaluations indicated that all participants felt it affected their practice in a positive way (144). In 1998, the Department of Veterans' Affairs implemented a project to help faculty in internal medicine training programs develop and implement state-of-the-art care for veterans at the end of life (145).

Perhaps the most innovate approach to faculty development was a report by Bruera et al. on patient-based learning offered through "bus rounds" (146). Participants used buses to take them on home visits to patients in palliative care home programs. During the bus ride between home visits, they discussed patients who they were to visit and reviewed relevant journal articles.

INTERDISCIPLINARY TRAINING

A common recommendation in palliative care is that education should take place in a multidisciplinary or interdisciplinary context. "A multidisciplinary field of study refers to an inquiry involving a plurality of disciplines in which disciplinary boundaries are maintained and the unique contributions of each are highlighted" (148). Clinicians who work in the multidisciplinary model are each representatives of a specialty, and they approach the patient's problems from their discipline's perspective. In contrast, interdisciplinary work can be thought of "as an inquiry involving a plurality of disciplines where disciplinary boundaries are often muted and the joint contributions of the synergy are highlighted . . . interdisciplinary activity emphasizes integrated, emergent approaches" (147).

It has been suggested that the *transdisciplinary* model should supplant the interdisciplinary. Transdisciplinary work has been defined as "a process by which researchers work jointly using a shared conceptual framework that draws together discipline-specific theories, concepts, and approaches to address a common problem" (148). Transdisciplinary education would seem an ideal model for palliative care. The evolving palliative care curricula provide the shared conceptual framework that could pull together the diverse fields of ethics, pharmacology, neuroscience, physiology, health services research, medicine, nursing, social work, psychiatry, chaplaincy, and clinical pharmacy to approach the relief of suffering.

These different models create uncertainties for educators in palliative medicine. To achieve the goal of collaboration with and respect for other disciplines, do physicians simply need training in how to work on a team composed of nonphysicians or should they have actual experience working as part of a clinical team? If clinical exposure is desired, is it sufficient to have a trainee (medical, nursing, social work) attend an interdisciplinary team meeting, or work with individual members of the team and then attend the meetings, or should trainees study together in a multi-, inter-, or transdisciplinary palliative care consult service, inpatient unit, or hospice?

In community and rural health delivery, interdisciplinary training has been effective in enhancing medical and nursing students' and allied health professionals' attitudes towards the professional range and competence of the other discipline (149,150). However, the authors of a Cochrane analysis of interprofessional education found only two intervention studies suitable for inclusion, although they are preparing a companion, less restrictive review (151,152 and 153). Despite the lack of data, the use of multi-, inter-, or transdisciplinary teams for training is often recommended in palliative care, and many of the courses described earlier (and others) are based on a model of multi-or interdisciplinary education (3,66,154,155,156,157,158 and 159).

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61

STAFF STRESS AND BURNOUT

MARY L. S. VACHON

Caregivers strive to provide palliative care through the com-prehensive management of the physical, psychological, social, spiritual, and existential needs of patients and families facing incurable progressive illness. The stress caregivers experience can be both extremely challenging and very rewarding. Care-givers who begin their encounters with patients at earlier phases of illness, when there is still the hope for cure or pro-longed survival, may find themselves connecting at a deep level with patients and their families. These caregivers may experience a roller coaster of emotions that may be similar to those experienced by patients and their families if and when the disease progresses. Caregivers may find themselves engag-ing in anticipatory mourning, questioning the appropriate-ness of some treatment protocols, or pushing to do anything to ward off impending death. Caregivers entering into rela-tionships with patients and families at a later point in the ill-ness continuum may feel they do not have the time they need to develop the relationship they believe would be most benefi-cial to help patients deal with their rapidly approaching deaths. They may feel that patients and families have come to them out of the limitations of the health care system, rather than through choice. Both groups of caregivers may have dif-ficulty dealing with issues of financial constraints in today's health care system. There also can be controversy about who should be the primary caregivers of people with advanced dis-ease— oncology staff, or palliative care or hospice staff.

This chapter provides a brief historical overview of the lit-erature on occupational stress, burnout, and compassion fatigue; highlights the personal and occupational variables that may lead to stress, burnout and compassion fatigue in palliative care; elucidates some of the satisfactions associated with palliative care; and discusses coping in these fields. The emphasis is on research from the previous decade. Discussions of previous research have been published elsewhere (1,2,3,4 and 5).

INTRODUCTION AND HISTORICAL OVERVIEW

Caregiver Stress

Interest in the issue of professional caregiver stress dates from the late 1950s. The psychologist Herman Feifel (6) noted that physicians were found to have a greater fear of death than laypersons. In the same year, the sociologist Renée Fox (7) studied the stress experienced by physicians conducting pioneering work on the artificial kidney and kidney transplantation. Intervention to assist with the man-agement of stress began with nurses (8,9), moving on to teams (10), and then to physicians (11). Most of the early work was anecdotal in nature and made no attempt to define or measure the stress experienced by staff, much less to document ways of managing such stress.

The hospice/palliative care movement began in England in 1967 and in North America in 1974, and interest in the area of caregiver stress burgeoned (1). Gradually, work emerged that focused on measuring and managing staff stress in both hospice and oncology settings (12,13).

Concept of Burnout

As interest in caregiver stress increased, the concept of *burnout* was elucidated. The term is generally credited to Freudenberger (14,15). Burnout has been characterized as “the progressive loss of idealism, energy and purpose experi-enced by people in the helping professions as a result of the conditions of their work” (16, p. 14). Burnout has also been described as a syndrome of responses involving increased feelings of emotional exhaustion, negative atti-tudes toward the recipients of one's service (depersonaliza-tion), a tendency to evaluate oneself negatively with regard to one's work, and a feeling of dissatisfaction with accom-plishments on the job (17,18,19,20 and 21) (Table 61-1). Pines (22) suggests that “the root cause of burnout lies in people's need to believe that their life is meaningful, and that the things they do—and consequently they themselves—are impor-tant and significant” (22, p. 633).

Burnout is associated with:
Overfunctioning behavior and issues from childhood
Work overload
Role ambiguity
Role conflict
Time and staffing limitations
A stressful, discouraging work environment
Lack of advancement opportunities
Poor working relationships
Lack of chairperson and peer support
Poor head nurse leadership style
Increased demands by patients and families
A failure to do work the way one feels that it “should be done”
A lack of a sense of meaning from one's work
Frequent exposure to death and dying
A lack of existential significance

Modified from refs. 18–21.

TABLE 61-1. BURNOUT AND WORK ENVIRONMENT

The term *compassion fatigue* (23) has been used to describe a syndrome that shares some characteristics with burnout: depression, anxiety, hypochondria, combative-ness, the sensation of being on “fast forward,” and an inability to concentrate. Garfield states, however, that in contrast to one who has burned out, the caregiver with compassion fatigue can still care and be involved (5,24). Given that most of the research on these topics has been done using instruments to measure burnout, this concept is addressed in more detail than is compassion fatigue.

Burnout is generally seen to result from the interaction between the needs of a person to sacrifice himself or herself for a job and a job situation that places inordinate demands on an individual. The person prone to burnout is apt to have unrealistically high personal expectations for satisfaction in a given area of life. The phenomenon can occur not only in an individual but also within a system (16,25). Pines (19) proposed a social-psychological model of burnout positing certain characteristics of the work environment as contributing to burnout. According to her model, professionals with a high level of motivation can either achieve peak performance, if working within a positive environment, or develop burnout symptoms, if the individual continues to confront a stressful, discouraging environment. Individual differences determine how soon an individual develops burnout and how extreme the experience might be.

Pines (20) has also written about burnout from a psychoanalytic-existential perspective. Psychodynamic theory contributes the idea that people choose an occupation that enables them to replicate significant childhood experiences, and existential theory suggests that people attempt to find existential significance through their work.

Pines suggests that unconscious images from childhood influence one's career decisions. “People choose an occupation that enables them to replicate significant childhood experiences, gratify needs that were ungratified in their childhoods, and actualize occupational dreams and professional expectations passed on to them by their familial heritage” (20, p. 634). Given that the choice of a career involves such significant issues, caregivers enter their careers with very high hopes, expectations, ego involvement, and passion. If one is successful in one's career, then one derives a sense of existential significance and partially heals one's childhood wounds. When one feels that one has failed to do the work the way it “should” be done, or when work does not give one's life a sense of meaning, then individuals burn out. A lack of existential significance is the hallmark of burnout (20).

Grosch and Olsen (21) also posit an interplay between systemic factors and personal factors that produce burnout to understand burnout in clergy. Many of the same dynamics may be at play with health care professionals. Self-psychology provides an understanding of a faltering sense of self, the regulation of self-esteem, and the deep longing for appreciation that contributes to burnout. Finding healthy ways of maintaining a strong sense of self is necessary for effective helping as a professional. Self-psychology suggests that many helpers were sensitive and alert children who learned quickly to adapt to the needs of their parents (26,27). “They then were able to give their parents all the attention and affection that the parents themselves missed as children. Consequently, these children's own needs, programs, blueprints, or scripts were not allowed to develop. The ultimate outcome of such situations is a predisposition for diminished self-esteem and repeated attempts as adults to find the 'ideal parent' in their own children or partners” (21, pp. 20–21)—or patients. The emotionally vulnerable professional, craving admiration and appreciation, may develop an ever-increasing workload of patients and become dependent on the need to be needed that feeds the professional's sense of self-worth. This overfunctioning behavior often develops in childhood. Indeed, those who choose medicine have been found to have strong obsessivecompulsive personality traits that lead them to “choose a career in which long hours of study, heavy responsibility and devotion to work are required. In fact, the more these traits are exaggerated the more outstanding a student may be” (28, p. 647, references in original).

THE INDIVIDUAL AND THE WORK ENVIRONMENT IN ONCOLOGY

Demographic Variables

Younger caregivers have been found to report more stressors, more manifestations of stress, and fewer coping strategies (29). In a UK study comparing clinical oncologists (formerly known as radiotherapists), medical oncologists, and palliative care specialists, burnout was associated with being younger than 55 years of age (30). When this study was expanded to include other hospital consultants (gastro-enterologists, surgeons, radiologists, and oncologists), being 55 years of age or younger was identified as an independent risk factor for burnout (31). Increased job satisfaction was found to be associated with older age (32), although older staff members may be more sensitive to a gap between their real and ideal work situation and, if such a gap occurs, older caregivers might be more vulnerable to stress reactions (33).

Santos and Cox (34) compared intergenerational differences in pediatric nurses in the workplace and found difficulties with work adjustment amongst “Baby Boomers” (born between 1946 and 1964). When compared with “Generation Xers” (born between 1965 and 1981) and “The Matures” (born between 1909 and 1945), Baby Boomers had significantly higher mean scores on *role overload*, in which resources exceed demands, and *role boundary* issues involving conflicting demands and loyalties. The Matures had difficulty with *role insufficiency*, in which training and skills exceed job demands. Generation Xers had the highest mean scores on *physical environment,* in which the workplace itself provides extreme conditions. Boomers had more difficulty with *vocational strain* problems with the workplace and *interpersonal strain*, disruption with interpersonal lives. The stress and strain scales tended to be more negative on three of the four scales for Boomers. *Self-care,* personal activity to reduce stress and social support, and having others to support you were highest in the Matures. Boomers had the lowest, most negative scores.

It is interesting to compare the latter study with Vachon (29), in which those older than 45 years had the least stress and most successful coping mechanisms and those younger than 30 years had the most stress and fewest coping mechanisms. The group that would have been the youngest part of the sample and the middle part of the Vachon study would be the Boomers, who are now having the most difficulty in the Santos and Cox study. The fact that those older than 55 years in the UK study (30,31) were least likely to experience burnout also gives some credence to this hypothesis. This phenomenon may be worth further study to ascertain whether this is an age cohort issue.

In the Santos and Cox study, Boomers had severe conflicts with the Xers. The themes that emerged involved orientation toward work, length of service, and workplace behavior. The Boomers interpreted the Xers workplace behavior as reflecting slacker attitudes and a lack of commitment. In addition, the Xers were considered to be arrogant and self-absorbed, and too apt to leave the work situation. The Xers did not have the same feelings toward the Boomers. They voiced great commitment to the profession and organization, but many anticipated leaving the institution at some point in the future, and perhaps even leaving the profession entirely at some point in their careers to develop a more diversified job skill set. They felt that the arrogance perceived by the Boomers was not actually arrogance, but rather the self-reliance they have had to develop throughout their lifetimes.

Gender has also been found to influence response to stressors in the workplace. Female physicians were found to experience more role strain than their male counterparts (35), and in a Canadian study were more likely to report suicidal ideation (36). In a large study of almost 2000 British family practitioners (37), male physicians had higher anxiety scores than the norms and had less job satisfaction and drank more alcohol than their female counterparts. Dealing with death and dying was not a major source of stress; however, it was associated with excess alcohol use, especially for female physicians.

Female physicians have been found to report greater job satisfaction and greater well-being than matched controls (37). The latter finding was replicated in the more recent Physician Worklife Study (N = 5704) (38). Women were more likely than their male colleagues to report satisfaction with their specialty and with patient and colleague relationships, but less likely to be satisfied with autonomy, relationships with community, pay, and resources. Female physicians were also more likely to report less work control than their male counterparts regarding day-to-day aspects of practice, including volume of patient load. In addition, they were not paid as well. There is some evidence that female physicians may be more at risk of mental health problems (39). In The Physician Worklife study (38), women were 1.6 times more likely to report burnout than men. The odds increased by 12–15% for each additional 5 hours worked per week over 40 hours. Lack of workplace control predicted burnout in women, but not in men. Women with young children who received support for balancing their lives from their partner, significant other, and colleagues were 40% less likely to report burnout.

Contrary to other studies, male, but not female, oncologists were at more risk of burnout in a Finnish study of physicians from many specialties (40, adapted from 3,41). Being married and having more children was associated with better job satisfaction in a Swedish study (32). Being single was an independent risk factor for burnout in the study of consultants in the United Kingdom (31).

Personality Variables

In looking at the stress of those working in palliative care, the personal characteristics that professionals bring to their profession are relevant, as is the impact of professional training programs. Hospice workers have been found to ground their work in self-awareness and a clear personal philosophy (42). Working with dying patients has been found to shape one's attitude toward death and dying (43). Those who coped adequately with death were found to have a tendency to live in the present, rather than the past or future. They scored higher on inner-directedness, selfactualizing value, existentiality, spontaneity, self-regard/ self-acceptance, acceptance of aggression, and capacity for intimate contact (44, from 41).

Research on the personality of oncology nurses using the Personal Style Inventory (45), based on the 1923 work of Jung (46), showed that the most common personality type for oncology nurses was introvert, seeker, feeler, judger (ISFJ), in which feeling is introverted and perception is practical, so that helping others is both a responsibility and a pleasure. Caregivers with these personality characteristics. value interpersonal interactions and have great empathy. The strengths of this personality type include independence, ability to work alone, diligence, and attention to detail. Traits that could be a hindrance include the proclivity to work alone and the tendency to act on internal reasoning without consulting others. The latter personality trait could be a problem because oncology nurses play a pivotal role in collaborative groups in today's health care environment. The introvert prefers quiet time to concentrate and think before making decisions. This personality type also dislikes interruptions, which can be a problem in the busy oncology clinic or unit (47).

The personality of physicians and its association with possible job stress and burnout has been mentioned previously. Kash and Holland (28) have noted that the compulsive tendency of physicians, “when present in conjunction with other characteristics of overly controlled emotions and low need for relaxation and pleasure, makes the medical student, and later the physician more vulnerable than others to depression, alcoholism, psychiatric disorders, and suicide” (28, p. 647). Such problems have been found to be associated more with adjustment before medical school than to occupational adjustment (48). Physicians with the least stable childhoods and adolescent adjustments have been identified as being most vulnerable to occupational hazards (48). When a faulty sense of self-esteem develops in childhood, the adult may be emotionally fragile and have easily threatened self-esteem or a heightened sensitivity to slights, disappointments, or rejections (21).

The personality characteristic of hardiness, which consists of commitment, control, and challenge (49,50), has been found to be associated with decreased rates of burnout in intensive care unit (ICU) nurses and with improved coping in house officers at Memorial Sloan-Kettering Cancer Center (MSKCC) (28). Hardiness was also found to be associated with decreased burnout in Greek oncology nurses (18). The sense of control over things that happen in life and in the work environment was found to protect nurses from emotional exhaustion, depersonalization, and a lack of personal accomplishment. Nurses who experienced a higher degree of burnout reported a lack of a sense of control over external events. In an American study (51), nurses who were high in hardiness had a predicted mean burnout score 0.468

less than those low in hardiness.

In a study of 1925 white and blue collar university employees in Australia (52), *Cognitive Hardiness,* which assesses involvement, challenge and control (53), was found to be the best predictor of the ability to manage job stress, anxiety, daily hassles, and to maintain a healthy lifestyle. Hardy behaviors depend on both behavioral competence and supportive environments. These variables allow the individual to find the resources essential to coping, to make use of social networks when needed, and to transform stressful experiences into meaningful experiences (54). Stressors are seen as manageable by those who are hardy (51).

Closely aligned with the concept of *hardiness* is the *sense of coherence* (55,56). The sense of coherence is defined as ". . . a global orientation that expresses the extent to which one has a pervasive, enduring though dynamic feeling of confidence that one's internal and external environments are predictable and that there is a high probability that things will work out as well as can reasonably be expected" (55, p. 23). With a sense of coherence, the location of power is seen as being where it legitimately should be. That may involve the individual being in a position of power, or it may involve power being vested in someone else, but the sense is that power is where it belongs.

A sense of coherence is partly personality-related and partly developed through life experience. It refers in particular to personal resourcefulness. Those with a broad repertoire and good flexibility are better able to adjust to most life challenges than those with poor repertoires (57). "(T)he sense of coherence (SOC) construct is a generalized orientation toward the world which perceives it, on a continuum, as comprehensible, manageable, and meaningful" (56, p. 15). The strength of one's sense of coherence is a significant factor in facilitating the movement toward health.

Antonovsky (55) distinguishes between a sense of coherence and a sense of control that implies that "I am in control." He states that a sense of coherence does not imply that one is in control; rather that one is a participant in shaping one's destiny, as well as one's daily experience (29). In the case of palliative care staff, the sense of coherence implies that caregivers have some ability to influence the care that their clients receive—for some, their influence may be great and for others, it may be more minor because of circumstances beyond their control—but they are able to make a difference.

Organizations exert a strong collective influence on the values, beliefs, and behavior of individuals (58). If staff members, as individuals, do not have a strong sense of coherence; if they are working in a setting in which they consistently find themselves having a lack of control; and if they do not have the sense that those in positions of authority know what they are doing and understand the reality of the world of the palliative care practitioner, the stage is set for feelings of powerlessness (5).

Stressors in Supportive and Palliative Care

Florio, Donnelly, and Zevon (59) studied 59 oncology nurses using a transactional model of stress, which views stress as a transaction between the person and the environment that is mediated by two processes: cognitive appraisal and coping. They developed a work-related stress concept map for oncology nurses involving the spatial relationships among nine stress clusters. "Physician-Related Stress" and "Ethical Concerns" were in close proximity to one another and composed the larger dimension of role conflict. "Death and Dying" and "Observing Patient and Family Suffering" were in close proximity and represented the emotional. stress associated with oncology nursing. The personal impact of stress was represented by the clusters "Carryover Stress" and "Negative Self-Thoughts," which are very close together. Finally, "Organizational Factors," "Coworker Stress," and "Inadequate Resources" were in close proximity and related to stress from the work environment.

"Organizational Factors," "Death and Dying," "Observing Patient and Family Suffering," "Physician-Related Stress," and "Ethical Concerns" were the most frequently occurring stress clusters. "Organizational Factors," "Observing Patient and Family Suffering," and "Physician-Related Stress" were rated as the most intense stress clusters. The least controllable stress clusters were "Organizational Factors," "Physician-Related Stress," and "Ethical Concerns." The most controllable stress clusters were "Carryover Stress" and "Negative Self-Thoughts." The authors conclude that oncology nurses experience high levels of emotional stress.

Emotional Labor

Work in palliative care can be described as *emotional labor*, which is "the labor involved in dealing with other people's feelings, a core component of which is the regulation of emotions" (60, p. 15). This work is often performed by women. "Emotional labor is hard work and can be sorrowful and difficult. It demands that the laborer give personal attention, which means that they must give something of themselves, not just a formulaic response" (60, p. 19). Such work also involves the regulation of emotion between the carer and the person being cared for, which is one of the sometimes tremendous but rewarding challenges of work in oncology.

When Swedish nurses working in hospice and oncology were compared (61), the content and quality of the nurses' physical and emotional labor differed significantly. Hospice nurses spent significantly more of their time with patients and relatives (37%) compared with the oncology nurses (21%). When they were with patients, most of the nurses' care involved physical activities, such as helping patients with their daily activities in hospice and helping patients with needs in relation to investigations and treatment in the oncology unit. The emotional labor of talking with patients and providing emotional support consumed 9% of the hospice nurses' time and 4% of the oncology nurses' time. These figures compared favorably to those of Quist (62), who found that emotional labor consumed only 2.3% of nurses' time. The proportion of direct-care time taken up by emotional labor was 19% in the oncology nurses and 24% in the hospice nurses, compared with 5.5% of the time in Quist's study. The authors compare this study with observational studies in an oncology unit in Denmark (63) and an acute and long-term care unit in Sweden (64). In both of the studies, the investigators found a discrepancy between the nurses' thoughts and actions. In their communications, the nurses were dedicated to patient-oriented and holistic care, but in their actions they prioritized routinized task or social and professional interactions with colleagues. During quiet working days, rather than engaging in the emotional labor to which they were committed, the nurses used their time in other ways. It was hypothesized that this was a way for the nurses to maintain control. "By minimizing their social relations with patients and routinizing their work, by working according to an agreed rule for a 'busy day,' the emotional involvement stemming from being too close to a patient could be controlled" (61, p. 72). The authors acknowledge that one of the limitations of the study is that it is not always possible to separate emotional labor from physical labor.

In a Bavarian study (65) comparing 57 physicians and 91 nurses on cancer wards in 13 settings, nurses were found to report greater stress and to have a vulnerability to stress in areas involving the empathic component of their relationship with patients. Physicians had stress associated with decision-making and communicating diagnoses. Having to work with trainees was seen as a stressor for both nurses and physicians. Small hospitals engendered less job critique among nurses, but more stress through identification with patients. Doctors found such hospitals to be cramped. The variables in this study were not linked to gender, with the exception that females of both professions had a greater tendency to cry. With age, stress reduced for most stress areas, as was found previously (29).

Mount (66) delineated the stressors of oncologists as including exposure to death as an existential fact, emphasizing the finite nature of life; the cumulative grief associated with repeated unresolved losses; the pressures of a medical care system fueled by the medical information system; the inability to achieve the idealistic goals embraced by holistic medical care; the stressors inherent in working as a team; and the issues involved in treatment failure. In a large study of physicians in the United Kingdom, clinical oncologists, formerly known as radiation oncologists, reported that most stress of their stress evolved from treatment toxicity and errors and from dealing with patient suffering. Medical oncologists reported more stress from organizational responsibilities/conflicts. Palliative care specialists had the lowest mean percentage of items contributing "quite a bit" to "a lot" to stress (30). The palliative care physicians reported that feeling overloaded, and the effects of this on their home lives, made the greatest contribution to their stress. Compared with other physicians, palliative care physicians reported less stress from overload and more satisfaction from having good relationships. They also reported less stress and more satisfaction with the way they were resourced and managed—unless they were hospital-based, in which case there was more stress and less satisfaction from management and resources (39).

Role Overload

Role overload was identified as a major issue for oncology nurses in the 1990s (67). In a study involving a random. sample of hospice nurses throughout the United States, job pressure—involving on-call duty, the need to travel to patients, and repeated crises—was one of the least appealing aspects of hospice nursing (68). The pressures of practice and work overload were associated with stress and burnout (29). Grunfeld et al. (69) studied 681 physicians, allied health professionals, and support personnel in Cancer Care Ontario. High job stress was associated with having too great a volume of work, having inadequate time to do the job properly, feeling under pressure to make deadlines, having conflicting demands on time, and having home life disrupted because of working long hours.

Oncology nurses experience difficulty with excessive demands, negative expectations from patients/families, unexpected crises, poor staffing, overwork, inadequate time, patient deaths, and balancing work and personal life (47). In a Swedish study, hospital nurses' heavy workloads kept them from being able to attend continuing education courses to learn how to deal with the problems they were experiencing (32). In another study, the more patients for whom the oncology nurse was responsible, the greater was her burnout score (33). Heavy workload was the only job stressor associated with burnout with emotional exhaustion being a particular stressor, in a study of Greek oncology nurses (18, adapted from 5).

Hospice initially prided itself on having time to spend with patients and their families. However, with financial constraints growing increasingly tight, hospice nurses are finding themselves more and more stretched to provide the type of care they want to provide. Further role overload could result if the potential for palliative care were ever to be realized. In one section of the United Kingdom, it was predicted that an increase of around 65% of inpatient provision would be needed to accommodate all

patients with chronic, progressive disease (70).

Role Conflict

Role conflict in palliative care can evolve from a variety of sources when one's role as a team member is in conflict with what one thinks might be in the best interest of patients. Such issues include conflict about end-of-life care between nurses and physicians; conflict with patients who may not yet be ready to accept the reality of impending death, when the nurse feels it is time for them to stop aggressive treatment (71); “allowing” patients to maintain control, while feeling disappointed in not being able to fully discuss patients' expressed wishes to die; taking actions to help patients or families maintain a sense of control, while questioning the wisdom and morality of their decisions; dealing with the sometimes hazy distinction between patient autonomy and a professional ethic of care (72); and the decision to transfer patients from active treatment settings to hospice or palliative care programs primarily for economic reasons (73). Inexperienced nurses caring for very symptomatic palliative care patients in the community may feel role conflict between the patient's right to good symptom control and the nurse's fear of hastening the patient's death (74).

Hart et al. (72) used critical incidents from the practice of palliative care nurses to improve skills in psychosocial care. They found that in the practice incidents that nurses identified, they repeatedly related roles in which they were mediating in a conflict situation to restore harmony and control. “The conflict was experienced within themselves and with others; the sense of control related to themselves, their clients and involved family and friends. Despite the magnitude of the issues they faced and perceived organizational constraints, most of the nurses related a sense of personal responsibility to mediate a successful outcome to the situation. When they were not able to 'fix' a situation, they expressed feelings of professional inadequacy” (p. 253). The nurses reported difficulty with patients who chose not to communicate their feelings about death and dying with either staff or their families and those who chose not to take medications so that death might come more quickly. Patients' actions to take “personal control” of their situation and to refuse palliative care threatened the nurses' feelings about their role as palliative care nurses and made them feel they had not been good enough advocates for palliative care.

Staff can also feel conflicted with the increased use of technology in palliative care. Staff in a children's hospice were studied in the early years of the program (75), as well as more recently (76). Whereas in the first study staff felt a sense of impotence when they were unable to relieve the perceived needs or distress of patients, in the second study they had concerns about the increasing use of life support equipment for the children, and the balance between quality of life and technical support.

Issues of Power and Control

Issues involving power and control in palliative care can be significant. There is some suggestion that conflict between oncologists and oncology nurses has decreased, possibly due to changes in pain and symptom control management (67). However, the struggle around power, a lack of control, and decision making in the British context is reflected in the fact that hospice medical directors rated their relationships with matrons as being most problematic (77). Encountering difficulties in relationships with nurses was the only aspect of work in which palliative care physicians reported more stress than their colleagues in other specialties. This was hypothesized to derive in part from the lack of role clarity in the roles of consultants and senior nurses in palliative care, because historically some charitably funded hospices were run by matrons (39). These issues are also being experienced in North America, as trained palliative care physicians attempt to integrate into preexisting hospice programs

Nurses report being in situations both in the hospital and in the community in which they feel responsible for alleviating the pain of a palliative care patient yet do not have a physician willing to order the medication they believe will be sufficient to control the pain. In addition, with the earlier discharge of sicker patients, nurses with limited experience may be expected to care for seriously ill palliative care patients in their homes, without access to physicians skilled in effective palliative care and symptom management (5).

Team Conflict

Team communication problems have been a significant part of hospice, palliative care, and, to a lesser extent, oncology since the early days of these specialties. The research on this subject has been reviewed elsewhere (1,5,78). A lack of support from one's team members has been associated with high levels of depression (79). Organizational factors, such as personality issues and team conflict, were more commonly reported stressors than were problems in dealing with patients and families and issues related to death and dying (29). This finding has recently been replicated in a study by Florio et al. of oncology nurses (59) referred to in the section Stressors in Supportive and Palliative Care.

Is Stress Greater Among Those Providing Palliative Care?

In a British survey (30) sent to all consultant nonsurgical oncologists in the United Kingdom, the stressors of medical oncologists (N = 69), clinical oncologists (formerly known as *radiotherapists*) (N = 253), and palliative care specialists were assessed (N = 126). Sources of stress were segregated into four factors: feeling overloaded and its effect on home life, having organizational responsibilities/conflicts, dealing with the patient's suffering, and being involved with treatment toxicity and errors. Clinical oncologists were more likely to experience burnout. In addition, they reported significantly higher stress from treatment toxicity and errors, and dealing with patient suffering, than medical oncologists, who reported more stress from organizational responsibilities/conflicts. Palliative care specialists generally reported the lowest mean percentage of items rated as contributing “quite a bit” or “a lot” to overall job stress. The estimated prevalence of psychiatric disorder in the physicians studied was 28%, which was similar to that of British junior house officers. The percentage of clinicians reporting high levels of exhaustion on the Maslach Burnout Inventory (MBI) was similar to that of the normative sample (31% versus 33%) (80). Thirty-three percent of both the cancer clinicians and the normative sample reported low personal accomplishment. Significantly fewer of the UK cancer clinicians reported high levels of depersonalization compared to the U.S. sample (23% versus 33%, p <.0001).

When these figures are compared with the recent Cancer Care Ontario study (69), the comparable figure for physician exhaustion was a much higher 53.3% (allied health professionals, 37.1%; support staff, 30.5%). A much higher 48.8% of physicians reported low feelings of personal accomplishment (allied health professionals 54%, support staff 31.4%). The feelings of depersonalization in the Canadian group were similar to the UK sample, with 22.1% of physicians (4.3% of allied health personnel and 5.5% of support staff) reporting feelings of depersonalization. These figures may be unique to Ontario, or may indicate an increase in stress in oncology due in part to everincreasing workloads and limited resources. At the time of the study, and for a period of years before the study, Ontario has been experiencing limited resources and treatment delays that are no doubt at least part of the source of the stress being experienced by physicians.

With regard to nursing staff, Cohen et al. (81) reviewed the literature and suggested that when comparisons were performed, oncology nurses differed little from, or fared better than, other nurses in terms of stress levels and stressors identified. The data from the Ontario study would indicate, however, that there is concern regarding the low feelings of personal accomplishment being reported by more than half of the allied health personnel (including nurses, social workers, and radiotherapy technologists) in this study.

Van Servellen and Leake (82) compared 237 nurses from acquired immunodeficiency syndrome (AIDS) special care units, oncology special care units, medical ICUs, and general medical care units and found no significant differences in scores on the MBI. They found that greater job influence had a significant protective effect on emotional exhaustion and enhanced personal accomplishment, and that job tension was a significant predictor of exhaustion.

In a Greek study, Papadatou et al. (18) found no statistically significant difference in burnout scores between oncology nurses and nurses in general hospitals. Personal characteristics were found to predict a greater percentage of variability in the burnout experience than either occupational or demographic variables.

In a British study, Wilkinson (83) measured the anxiety of 65 nurses working on six units in two cancer hospitals. The Spielberger State-Trait Anxiety Inventory (84) was used. Oncology nurses were found to be no more anxious than other working women. Newly qualified nurses were more anxious than sisters and enrolled nurses. Nurses who never went to church had a higher state anxiety score than those who went to church weekly or occasionally. There was some difference in the level of state anxiety on different wards and the authors noted that the ward on which nurses worked appeared to influence the levels of stress and job satisfaction experienced—this was thought to be due in part to managerial style affecting ward climate.

When the team in a hospital-based home care unit (HBHC) working with severely ill cancer patients was compared with the staff working with a similar population of patients on three inpatient units, both groups showed a limited degree of continuous stress and a high degree of job satisfaction (32). However, there were differences between the two work environments. The HBHC group reported more freedom to make their own decisions, better cooperation between day and night shifts, a more reasonable workload, fewer problems in communication with patients, and fewer problems with tension and sleeping. These findings were felt to be due to the fact that the HBHC team was older, more often married, and had worked longer in health care. They were thus more experienced.

A German study compared 299 physicians and 592 nurses from 54 different hospitals and clinics (85). The staff worked in oncology, cardiac, intensive care, or surgical units. Although the groups experienced the same overall degree of work-related stress and physical complaints, the oncology group suffered more from feelings of emotional involvement and self-doubt. However, the oncology group suffered less from stress connected with institutional factors than did the comparison group,

despite few objective differences in their situations. The author hypothesized that the stress accompanying the care of people with cancer is no greater than that which accompanies the care of other medically ill people but is of a different quality. For oncology staff, institutional stressors move into the background when compared with the personal emotional involvement of working with patients.

In general, although the stress of those in oncology in the 1990s did not differ significantly from that of their colleagues in other medical and nursing specialties, it was generally greater than that of colleagues in palliative care. The Ontario study (69) may reflect an increase in stress in oncology with increasing workloads and limited resources. In a review of the literature on stress in palliative care (1) it was concluded that, whereas in the early days of the palliative care movement stress was a problem, later studies have shown that stress and burnout are by no means universal. As we move into the new millennium and workloads are increasing, further research is needed to assess whether palliative care practitioners are also feeling the strain of this change. Of course, comparisons would then also need to be made with health care practitioners in a variety of other specialties whose workloads have increased.

Stressors versus Rewards

Although palliative care can be stressful, some authors have also tried to measure its rewards. Papadatou et al. (18) suggest that the challenge of working with cancer patients may serve as a reward that counterbalances the stressful aspects of practice. Bean and Holcombe (47) point out the way in which the personality types of oncology nurses may be complementary to the stressors identified in the work setting (47,86), leading presumably to increased job satisfaction. Some of the satisfactions that may be received from working in palliative care include

- Valuing each individual; experiencing the reciprocity of giving and receiving in relationships; having a sense of interconnectedness and of mutual nurturing; being close to patients and sharing a part of one's self; having the chance to make a difference in people's lives (87)
- Helping patients achieve optimum health by enabling them to do all they are capable of doing; being able to give patients options, recognizing that patients are the directors of their own decision making; being able to personalize the hospital environment so patients can feel more at home (87)
- Assisting patients and families learn to cope with and adjust to caring for a dying relative at home; managing death at home; learning from patients and families (88)
- Experiencing positive feedback from patients and families; effectively relating with and communicating with patients and families (89)
- Witnessing the smooth termination of life; initiating innovative, effective intervention for the patients, involving the right decisions at the right times; and peace for the patient (89)
- Being able to provide families with good memories in the midst of difficult times (89)
- Helping patients to find meaning in suffering (90)
- Having an opportunity to learn skills and to develop as a person; having the ability to constantly learn (87); finding the challenge of working with cancer patients to be a reward that counterbalances the stressful aspects of the work (18)
- Experiencing positive relationships and support from colleagues (81,89,91)
- Deriving satisfaction from the essence of oncology nursing, including handling emergencies, preventing serious errors, helping with emotional distress, and empathizing with patients (86)
- Dealing well with patients and relatives (30)
- Having professional status and esteem, deriving intellectual satisfaction, and having adequate resources to perform one's role (30,91, adapted from 5)

MANIFESTATIONS

In a study of more than 2000 Canadian physicians, those under stress had more problems with patients, obtained less satisfaction from their medical practice, and rated their quality of care lower (92,93).

Physical

A strong association has been found between specific, situational stressors and reported psychosomatic complaints (65). Interpersonal difficulties, whether on or off the job, related to physical distress for nurses, whereas for physicians, dissatisfaction with the job and working conditions, including space problems involving the work environment and dealing with patients, related to a general malaise. Irregular working hours related to stress in both groups.

Nurses were more apt to report problems with headaches/pressure in head, tiredness, tendency to cry, loss of appetite, irritability, and neck/shoulder pain if their lives outside the work situation did not relieve the stress generated on the job. For nurses, there were three distinct phenomena associated with the stress of dealing with patients: interpersonal conflict (leading to irritability and headaches); physical distaste for certain tasks (leading to visceral pain and nausea); and physical strain, causing back pain, heaviness in legs, and neck/shoulder pain. Identification with the patient correlated most markedly with tiredness in its various forms. If the reported symptom level, rather than the reported stress level, was taken as an indicator of objective stress, then neither lack of satisfaction with the job and the surroundings nor proximity to the dying was linked to health-related concerns. Identification with the patient's suffering was itself principally tiring. However, the effects of interpersonal difficulties *(private life* and *dealing with patients)* were most worrisome (65).

The authors observe that for physicians the findings can be summarized in one over-simple phrase: “Stressed doctors are tired” (65, p. 1017). For the physician group, the authors described a subpattern of symptoms that “linked stress to loss of control, in the form of irregular heartbeat, diarrhea, discomfort in the throat, dizziness, and breathlessness. The doctors' stress may derive in part from lack of confidence when faced with their limited ability to alter the course of illness. Identification with the patients' suffering, which was linked to tiredness among nurses, had effects among doctors that suggest an almost physical rejection of the patient” (65, p. 1021).

Psychological

Compassion Fatigue

Whereas health professionals traditionally have been taught to maintain a boundary between themselves and their clients, very close relationships can and do develop in palliative care and oncology (94). This closeness and exposure to repeated difficult illness experiences and deaths can lead to the experience of secondary traumatic stress (STS) or compassion stress. *STS* is defined as “the natural consequent behaviors and emotions resulting from knowing about a traumatizing event experienced by a significant other—the stress resulting from helping or wanting to help a traumatized or suffering person” (23, p. 7). Secondary traumatic stress disorder (STSD) is a more severe manifestation of STS and “is a syndrome of symptoms nearly identical to PTSD (posttraumatic stress disorder), except that exposure to knowledge about a traumatizing event experienced by a significant other is associated with the set of STSD symptoms, and PTSD symptoms are directly connected to the sufferer, the person experiencing the primary traumatic stress” (23, p. 8). Compassion fatigue is identical to STSD and is the equivalent of PTSD (, from). Garfield (24) writes of the compassion fatigue that exists amongst AIDS/human immunodeficiency virus caregivers. He states that in contrast to caregivers heading for burnout who unconsciously begin to wall off more and more strong feelings associated with their work, those with compassion fatigue are able to monitor their decrease in empathy and feeling and remain emotionally accessible. However, they have greater and greater difficulty in processing their emotions, are anxiety-ridden or distressed, and have images that intrude on their days and nights and painful memories that flood their world outside the caregiving arena (from 5).

Multiple Grief and Loss

Mount (66) has reflected on the losses associated with working in oncology and notes that these losses become an integrated part of one's professional life. “Moreover, our losses do not occur in a vacuum. They interact with, modify, and often augment the other stressors in our personal and professional lives. Our reaction to loss may be repressed, only to surface later, associated perhaps with some other unrelated event” (66, p. 1127). He warns that the weight of these losses may lead to a burden that is increasingly intolerable and frequently difficult to define.

Papadatou (95) has defined the losses in oncology nursing as follows:

- Loss of a close relationship with a particular patient
- Loss due to the professional's identification with the pain of family members
- Loss of one's unmet goals and expectations
- Losses related to one's personal system of beliefs and assumptions about life
- Past unresolved losses or anticipated future losses
- The death of self

Constant exposure to death and loss may leave caregivers with grief overload and considerable distress. However, participating in the death of some patients has been found to result in some nurses having intense positive responses that promote professional development (96). Constant confrontation with the deaths of others causes

caregivers to repeatedly reevaluate their own mortality and to reexamine the meaning of life and living (66).

Nurses have difficulty with grief if they had not been able to help the patient die a good death, for whatever reason (96). When the symptoms of dying patients are not controlled, the nurses feel responsible and “wanting,” and if training and experience are lacking, this may well be the case (74). Staff members often experience difficulty dealing with their feelings of grief and loss at the time of death because of other responsibilities that must be attended to immediately. There is often a strong covert institutional message, as well as peer pressure, not to dwell on the loss (97).

Particularly since the AIDS epidemic, the concept of multiple loss has been increasingly recognized. The concept of multiple loss in AIDS caregivers reflected in part the reality that many caregivers were caring for dying patients, while partners, friends, and members of their social network were dying at the same time.

Chronic compounded grief, defined as cumulative responses to losses over a period of time, has been found to be a powerful factor that contributes to resignations and turnover among oncology nurses and the ability of individual nurses to care for patients effectively. Feldstein and Gemma (97) suggest that what others refer to as burnout is really chronic compounded grief. In a study of response to death in a Canadian continuing care and rehabilitation hospital, 42% of the staff felt themselves to have been “moderately” to “extremely” affected by patient deaths, had lost time at work due to patient death, had low morale, experienced strain in personal relationships, had a loss of efficiency at work, or had health problems they attributed to patient deaths (98, from 5).

Burnout

In a large study of the stress of oncologists (99), 56% of oncologist subscribers to the *Journal of Clinical Oncology* Burnout was measured using an author-constructed questionnaire, as opposed to one of the more usual instruments used to measure burnout (100). When asked to define the specific nature of their burnout, 56% mentioned frustration or a sense of failure, 34% mentioned depression, 20% mentioned disinterest in practice, and 18% mentioned boredom. Almost half felt that burnout was inherent to the practice of oncology. Institution or university-based oncologists on salary reported a lower incidence of burnout (47%) than those in private adult oncology practice (63%).

In the Ramirez et al. study of UK oncologists and palliative care specialists (30), *job characteristics* associated with burnout included “being overloaded and its effect on home life,” “dealing with patients' suffering,” and low levels of satisfaction from “not having adequate resources to perform one's role.” Depersonalization was associated with “being overloaded” and “dealing with patients' suffering” as well as low levels of satisfaction from “dealing well with patients and relatives.” Being a clinical oncologist, as compared with a medical oncologist or palliative care physician, and working part-time, were independent risk factors for depersonalization. “Low personal accomplishment was associated with stress from 'being involved with treatment toxicity and errors' and low levels of satisfaction from 'dealing well with patients and relatives' and from 'having professional status and esteem'” (30, p. 1268).

A large Finnish study of 2671 physicians (40) found that male oncologists were among those physicians most likely to report burnout; the same finding was not reported for female oncologists. The authors speculated that higher burnout is associated with the specialties involved with dealing with chronically ill, uncurable, or dying patients. They hypothesized that hope (and the lack of it) in medical work has important influences on feelings of burnout. As with the U.S. study (99), they found that those with a university position were less likely to report burnout.

In the Papadatou et al. study of oncology nurses (18), only the stress of a heavy workload, among all the job stressors studied, was found to be associated positively with burnout (and emotional exhaustion in particular). This finding is similar to that reported by oncologists (99), although the self-controlled aspects of workload (e.g., involvement in research and teaching) may be negatively related to burnout (18). Among house staff, hardiness was found to be negatively related to burnout and physical illness; negative work stressors were positively related to burnout, as was supervisor support (28).

The finding that self-controlled workload may be negatively related to burnout is interesting in view of the fact that in a large study of professionals from a variety of settings, those in oncology were most apt to mention developing the multiple roles of clinician, researcher, and teacher as one of their major coping mechanisms (29).

Coping styles can exert a protective influence on burnout. In a group of nurses (51), those using direct, active coping (changing the stressor, confronting the stressor, finding positive aspects in the situation) had the lowest burnout scores, and those using direct-inactive coping (ignoring the stressor, avoiding the stressor) had the highest scores. The lowest burnout scores were found in nurses with greater hardiness who used direct-active coping behaviors.

Depression and Burnout: Do They Differ?

Feelings of depression must be distinguished from those of burnout. Maslach states that one phase of the burnout syndrome involves a sense of reduced accomplishment and a loss of self-esteem, which is a central characteristic of depression. The loss may be that of early ideals or of “good people” to work with. A professional's sense of self-worth and self-esteem may be threatened by the inevitable outcome of patients' deaths and the physical, psychological, and social pain of terminal illness (101). Caregivers may also feel that they have failed at their work or have failed to live up to their original standards (17). Burnout is generally regarded as being associated with overinvolvement in any one area of life to the exclusion of all others. Usually this is the occupational role (102).

Although the burned-out person may be depressed, the symptoms are not primarily intrapsychic but are, at least partially, situationally induced. An appropriate evaluation of burnout requires that the possibility of a clinical depression be ruled out. A clinical depression might be suspected if the person has had a recent loss, has the vegetative symptoms of depression, has had a previous history of depression, or has a family history of depression (102). If the symptoms are worse in the work situation, associated with conflict or feeling misunderstood by colleagues in a person who tends to work long hours or always takes work home and has no time for outside interests or support from others, then the problem may well be burnout.

Ramirez et al. (30) attempted to distinguish between the phenomenon of burnout and psychiatric disturbance. They used the 12-item General Health Questionnaire (GHQ) (103). The GHQ has been used in a variety of studies of occupational stress (see 1 for a review of its use in palliative care studies). The estimated prevalence of psychiatric disorders from the GHQ was 28% and was not significantly different among the three oncology specialty groups, nor did their findings differ from other studies (30). They concluded that although clinical oncologists experienced the greatest amount of work-related stress and lowest satisfaction from work-related sources, they are not at any greater risk of psychiatric disorder than their colleagues.

No demographic or job characteristics predicted psychiatric disorder as measured by the GHQ. However, high GHQ scores indicative of psychiatric disorders were associated with high levels of stress from feeling overloaded, being involved with treatment toxicity and errors, and deriving low levels of satisfaction from having professional status and esteem.

In an Italian study (91) comparing oncologists, nurses, and radiotherapy technicians, 16% of subjects reported depression on an author-constructed instrument. Nurses, women, and younger respondents were most likely to report depression.

COPING WITH STRESS AND BURNOUT IN PALLIATIVE CARE

The research on coping with job stress is still limited. There have been few long-term longitudinal studies of coping. In a multidisciplinary, multispecialty study, caregivers were twice as likely to report personal coping strategies, rather than environmental strategies, as being helpful in dealing with and preventing occupational stress (29). Florio et al. (59) compared positive versus negative outcomes of coping strategies using problem-focused versus emotion-focused coping strategies. The coping strategies that were most effective in handling work stress were *emotion-focused/positive* (develop a growth perspective, positive reappraisal, affective regulation and balancing work stress) and *problem-focused/positive* (including positive involvement in treatment and coworker support). Less effective strategies included *emotion-focused/negative* (withdrawal, apathy, negative coping, catharsis/break room).

Personal Coping Strategies

On the basis of the findings of the subsample of 110 professionals in oncology, the most helpful personal coping strategies included developing a sense of competence, control, and pleasure from one's work; having control over aspects of one's practice; having a personal philosophy of illness, death, and one's professional role; managing one's lifestyle; and leaving the work situation.

A Sense of Competence, Control, and Pleasure in One's Work

A sense of competence, control, and pleasure in work is often associated with a sense of belonging to a team “that knew what it was doing.” Through team affiliation one may derive an ongoing sense of personal worth that survives even though individual patients die (29).

A sense of competence is very similar to the sense of personal hardiness found to be helpful in other studies (18,28), as well as to the sense of coherence (55,56 and 57). Hardiness protected oncology nurses from emotional exhaustion on the MBI. The personality factors that best predicted personal accomplishment on the MBI included a sense of mastery and control over the difficulties of life and a problem-focused coping style when faced with adversity. The role-related variables that predicted high personal accomplishment included a tendency to assume somewhat neutral expectations (neither high nor low) regarding job satisfaction at the beginning of one's career (18).

A sense of competence can also be associated with having a good person-environment fit between one's personal characteristics and the work environment (29). Bean and Holcombe (47) noted the ways in which the personality types of oncology nurses were complementary to the essence of oncology nursing identified by the nurses in the Cohen and Sarter study (86). The introvert's attention to detail could prevent serious errors, which was viewed as a part of the essence of oncology nursing. The critical incidences of “empathizing with patients and helping with emotional distress were consistent with feeling as the preferred way of making judgments” (86, p. 1484).

A sense of control included redefining particular situations as being a challenge instead of a threat, redefining one's role and involvement with people (e.g., “It is not my role to save people from their illness; rather it is my role to help people to lift the burden which is theirs”), developing more complex skills, and sharing decision-making and control with patients (29). Antonovsky (56) noted that participating in trying to change difficult situations can prevent damage to an individual's sense of coherence, can sometimes add strength, and in some cases can create the opening for the beginning of a major change in life circumstances.

A sense of pleasure in one's work evolved “from one's work with individual patients, from pleasure in the utilization of professional skills, or satisfaction with the indirect impact that one's work can have on groups of patients and families that one might influence indirectly through teaching or administrative roles” (29). Caregivers reported allowing themselves to feel pleasure at a job well done. This approach requires a certain maturity, as well as an ability to distance oneself from the pain of others and to derive satisfaction objectively from one's role in helping to alleviate at least some of this suffering. Some caregivers have difficulty in distancing in this way and feel guilty if they experience a sense of satisfaction that is associated with the suffering of others. When individuals participate in changing conditions and in the process of changing societal conditions, such as has happened in hospice and is now happening in palliative care, there is an improvement in their sense of self-efficacy and self (5).

Perry (87) has used nursing narratives to explore exemplary nursing practice in palliative care and oncology nursing. She uses the themes of the dialogue of silence, mutual touch, and sharing the lighter side of life to illustrate aspects of exemplary nursing practice and identifies joint transcendence as the essence of exemplary nursing practice. “When both care providers and care receiver are co-participants in caring, the release can potentiate self-healing and harmony in both. The release can allow the one who is cared for to be the one who cares, through the reflection of the human condition that in turn nourishes the humanness of the care provider. In such connectedness they are both capable of transcending self, time, and space. Neither stands above the other” (104, p. 132 in 87, p. 100). Hart et al. (72) suggest that the reconstruction of nursing intervention through narrative gives meaning to the experience and creates opportunities for challenge and affirmation.

Barnard et al. (105) have used the narrative approach to study the process of hospice and palliative care from the perspectives of patient, family, and professional and volunteer caregivers. Their research shows clearly the points of tension that develop when patients, families, and caregivers disagree on the goals of care and how these issues are and are not worked out to the benefit or detriment of all concerned.

A Personal Philosophy

The caregiver who is going to stay in oncology for an extended period often feels the need for something beyond the present role. A personal philosophy of illness, death, and one's professional role is an important coping mechanism for many (29). “Becker (106) believed that people's need to believe that the things they do are meaningful is their way of dealing with the angst caused by facing their own mortality. In order to be able to deny death, they need to feel heroic, to know that their lives are meaningful, that they matter in the larger 'cosmic' scheme of things” (20). Becker spoke of the need for people to become heroes (106). The way they become “heroes” depends on “their culture's prescribed 'hero system.' In previous eras, religion was the most commonly chosen hero system. Today, for many people, religion is no longer adequate. For people who have rejected the religious answer to the existential quest, one of the frequently chosen alternatives is work. People who choose this alternative are trying to derive from their work nothing short of a sense of meaning for their entire lives” (20, p. 634). Existential quests are a way of coping with the fear of death (20). For some, a religious philosophy centered around a commitment to serve others may be both helpful and key to deriving a sense of meaning in difficult times.

Heim (35) found that religion could be a helpful coping mechanism for a certain group of nurses. The religious beliefs of house staff were also found to be associated with lower burnout levels (28). However, when caregivers use their own personal religious beliefs to reach out to patients, this may or may not be helpful to the patients (107).

For many caregivers, the concept of the “wounded healer” is an integral part of their philosophy of practice (24,108,109,1 and 110). This concept derives from ancient universal shamanic stories of Paleolithic times. These stories are of tribal priests, “the original wounded healers, whose ability to heal others was seen as being directly linked to their having journeyed in depth into their own wounded selves” (109).

Successful caregivers are often “wounded healers,” with wounds sustained in childhood, adulthood, or both. “In many cases, in trying to heal their respective wounds, these caregivers were drawn, consciously or not, to healing others” (107). Sulmasy (110), a physician, philosopher and Franciscan friar, contends that, “All health care professionals are wounded healers. They cannot escape suffering themselves. Moments of pain, loneliness, fatigue, and sacrifice are intrinsic to the human condition. The physician or nurse's own bleeding can become the source of the compassion in the healer's art. From the physician or nurse's own suffering can come the wine of fervent zeal and the oil of compassion . . . The physician's or nurse's wounds can become resources for healing” (110). Sulmasy warns, however, that wounded healers must not become so overwhelmed with the suffering of others that they are unable to offer effective care. “Competence remains the first act of compassion. Wounded healers do not ask their patients for help, but recognize the unity between their own neediness and the needs of their patients. Wounded healers issue an invitation to patients to enter into the space of the healing relationship” (110). In this sense, the clinician offers hospitality.

Henri Nouwen (108) wrote of the minister as a wounded caregiver. His perspective provides interesting reflections for caregivers in palliative care. Nouwen quotes the Talmud as asking the question of how one might know the Messiah. “He is sitting among the poor covered with wounds. The others unbind all their wounds at the same time and then bind them up again. But he unbinds one at a time and binds it up again, saying to himself, 'Perhaps I shall be needed: if so I must always be ready so as not to. delay for a moment' (taken from the tractate Sanhedrin)” (108). From Nouwen's perspective, the caregiver must bind her own wounds carefully in anticipation of the time when she will be needed. The wounded healer must look after her own wounds, but at the same time be prepared to heal the wounds of others (from 5).

Inherent in a philosophy of practice is the right, and indeed obligation, to mourn for those who have died. Although not all patients touch caregivers equally, in many situations patient deaths and the ensuing staff grief deserve recognition. Acknowledging the deaths of individual patients can enable practitioners to avoid the accumulation of grief that comes from repeated, unresolved losses (66). However, at times, multiple losses can lead to a sense of grief overload that may need to be dealt with in a variety of ways, including memorial services, journaling, staff “wakes,” or funeral attendance. In addition, participating in a grief process can enable caregivers to assess gains that have been made and what one has gained from this relationship in a manner that may be helpful to future clinical practice.

Management

Although lifestyle management is certainly not a panacea for dealing with work stress, it enables one to have the energy to cope with stressors. It reflects acknowledgment of an individual's need to learn his or her body's response to stress to detect signals of significant overload. When one finds oneself experiencing symptoms of stress, such as headaches, gastric disturbances, increased infections, a lack of pleasure in one's professional roles and responsibilities, or feeling overwhelmed by responsibilities, it is often time to take a break before symptoms become more serious. This break may consist of a few hours away from one's desk to pursue another interest or a longer break of a few days or weeks. Oncologists have suggested decreasing burnout through time away from the clinical setting, including more vacation or personal time and sabbaticals (99).

Effective lifestyle management involves developing a balance between one's personal and professional lives. Job-home interaction has been found to be a significant source of stress in several studies (29,30,65). Controlling jobhome interaction can be very difficult, particularly for those who have developed multiple professional roles (e.g., clinician, researcher, and writer) while trying to maintain a healthy personal life. Certainly, there are times in which career demands must take precedence, but if one always bows to career demands at personal sacrifice, one may need to do some looking at one's sense of self-esteem.

Although lifestyle management and good health habits, including diet, exercise, and rest, are all helpful in stress reduction (Table 61-2), those in oncology often do not mention using these coping strategies (81). For caregivers who are prepared to do some reflecting on their occupational roles and the meaning it has in their lives, the questions contained in Table 61-3 are helpful.

Other lifestyle management techniques that have been shown to be effective include the following:
Recognize and monitor symptoms
Good nutrition
Meditation
Spiritual life
Grieving losses
Decrease overtime work
Exercise—aerobic, yoga, qi gong, tai chi
Energy work—reiki, healing touch, therapeutic touch
Maintain sense of humor
Seek consultation if symptoms are severe
Discuss work-related stresses with others who share the same problems
Visit counterparts in other institutions; look for new solutions to problems
Time in nature (5,28,111)

TABLE 61-2. LIFESTYLE MANAGEMENT TECHNIQUES

Treating career burnout addresses three questions:
Why, psychodynamically, did this person choose this particular career, and how was it expected to provide existential significance?
Why does this individual feel a sense of failure in the existential quest, and how is the sense of failure related to burnout?
What changes need to take place for this individual to derive a sense of existential significance from work (20, p. 633)?

TABLE 61-3. TREATING CAREER BURNOUT

Social Support Systems

The development of a personal social support system to help to sustain one through life and its vicissitudes, both on and off the job, is extremely important. The following is a personal “tried and true” approach to aspects of a social support system that can be helpful in facing stress on and off the job and helping one to maintain a sense of roots:

- A spiritual life that connects the individual with the transcendent, from which one can derive a sense of meaning and purpose in life that can be sustaining even when personal and professional stress is at a high level.
- A solid, supportive family system comprised of people who can listen and provide emotional support, emotional challenge, and practical assistance.
- A network of friends comprised of persons who are involved in various aspects of one's personal and professional life, with whom one has reciprocal relationships and to whom one can turn for help in a variety of ways, and who in turn can look to you for such help.
- Supportive colleagues at work, whether those be team members; colleagues outside of one's direct team with whom one can share the trials, tribulations, and joys of the workplace; or administrators who can understand the stress to which one is exposed.
- Colleagues with whom one may not work but who understand one's professional trials and tribulations, with whom one can share a similar professional value system and from whom one can receive support. The author belongs to a support group of oncology nurses who have met every 6 weeks for 25 years. A group that shares personal and professional life experiences together such as this is of inestimable value.
- A community of others reflecting one's religious beliefs or value systems.
- A mentor or supervisor who can provide support and challenge and with whom, ideally, one can reflect over the years (112).

Organizational Coping Mechanisms

Team Philosophy, Team Support, and Team Building

Although personal coping mechanisms are important, the work environment does have a role to play in helping caregivers provide effective care to those with cancer. A sense of team philosophy, support, and team building has been identified as an important organizational coping mechanism for both palliative care and oncology professionals (29). Improving interprofessional cooperation, team processes, and group support in nursing was found to provide the best protective or buffering approach to many health stressors, especially burnout (35). The perception of social support at work was also correlated with lower burnout in a study comparing hospice and oncology nurses (33).

Nason (113) notes that team development always involves tension and conflict. This may be viewed as the result of competition, lack of role definition, or poor leadership, but it can also be viewed as a reflection of contradictory institutional goals. Team members may become entrapped in conflicting relationships through the interaction of limited resources, competing demands, and unrealistic institutional priorities, and as a consequence may come to represent differing value systems within the organization. For example, team members of different disciplines may become involved in rivalry and “turf wars” in the current tight economic climate in which the roles of many professional groups are being challenged.

An effective team must have clear objectives, mission, and priorities that are shared by all team members. Role expectations should be realistic and well defined when they overlap. Effective decision-making and problem-solving processes should be in place to arrive at the “best” possible solution; environmental norms should exist that support the tasks of problem-solving. There should be a concern for each other's needs and an opportunity for individuals to enlarge their roles and optimize their chances for personal growth (114).

Papadatou et al. (115) studied the role of social support in pediatric nurses in oncology and critical care and found that over time the role of colleagues became increasingly important; for some nurses this was the only source of emotional support. There was an intimacy that evolved involving friendships and quasi-family relationships outside of work and even marriage.

The support in that group of nurses was sought at four levels: informational, clinical/practical, emotional, and meaning-making. The first two levels of support primarily benefited the patient, whereas the latter two levels of support helped the nurses cope with the dying process and the death of children. There were similarities and differences in the levels of support used by both groups. Both groups valued *informational support,* although in different ways. Critical care nurses preferred information addressing clinical issues, whereas oncology nurses valued information exchange about the progress and treatment of individual patients and about acquiring new scientific knowledge. Both groups were dissatisfied with the *level of clinical/practical support,* primarily because of difficulty in cooperation among team members. In oncology, this involved difficulties with role blurring between physicians and nurses; in the ICU, it involved rivalry and closed subgroups due to educational differences. The two groups were also different in the receipt of *emotional support.* In the ICU the ongoing presence of several colleagues provided emotional and clinical support, whereas the pediatric oncology nurses were more apt to be without a colleague or physician at night. The oncology nurses were more apt to share emotions and experiences openly when a child died, whereas the ICU nurses shared primarily in small groups or with “friends.” They tended to try to avoid focusing on issues of death and to focus their energy on saving other children (5).

Support Groups

The development of supportive, collaborative work relationships may be fundamental to enhancement of selfefficacy and self-esteem. It is important that organizations create the opportunity for ongoing support, and that nurses have the time to attend support sessions, especially for those working alone in the community. This may consist of support through team meetings, easy access to consultants, a buddy or mentor system for ongoing support, and the opportunity to debrief after critical incidents (5).

Although support groups are recommended almost as a panacea for either team stress or problems with patients, they were found in one study to be the least commonly mentioned organizational coping strategy (29). Horowitz et al. (116) reported on interdisciplinary “pizza rounds” held weekly on the Neurooncology Service at MSKCC. The purpose of the rounds is to “enhance patient care by improving interdisciplinary functioning and by providing staff with the opportunity to exchange ideas, solve problems involving difficult patients and families, develop consistent plans for patient management, and ventilate their emotional responses to job-related stress. Food is served as a means of increasing attendance and reducing hierarchical barriers between staff members” (p. 330). The group is led by a social worker and a psychiatrist. Although no formal evaluation of the meetings has been conducted, the authors feel that the fact that the group has endured for a period of years attests to its effectiveness.

Administrative Policies

The incidents that cause problems for caregivers often reflect how organizational policies and practices limited the flexibility of staff to implement effective care (72). To support patient autonomy, nurses need to experience professional autonomy within the work environment. When they do not have this professional autonomy, they need to work towards achieving it, or recognize the limitations of the system in which they work and not assume personal blame and responsibility when this is inappropriate (5).

Effective administrators and administrative policies can be extremely important in maximizing productivity and job satisfaction. Oncology nurses valued administrators who were able and willing to change the work environment for staff. “Competent, caring administrators provided leadership, were flexible and available, communicated with staff, fostered development, and allowed opportunities for growth and input into decisions . . . Nurses spoke about how important it was to 'have a voice in fixing' a problem at work” (81). In view of the stress experienced by those in oncology because of work overload, it is important to develop realistic workloads that recognize the needs of both caregivers and organizations. Effective administrative policies need to recognize the importance of the emotional labor of oncology and to recognize that this activity sometimes takes time away from other activities (60).

An environment should be provided in which the feelings generated in oncology care can be recognized and expressed. James (60) warns that although the repression of emotion at work may appear to lead to greater efficiency in production, it does not mean that emotions disappear, merely that they are concealed but will eventually be expressed elsewhere—that is, at home or possibly in leisure pursuits. It takes time to work through frightening or worrisome feelings, helping ill people and their families to work out a strategy that they can live with. Time needs to be worked in to provide job flexibility to deal with emotional labor in a highly technological environment (60). By making the expression of feelings in the workplace unacceptable, labor processes may affect not only how feelings are expressed in the workplace but also the emotional labor that is likely to be necessary at home. In a Swedish study, a home-based care program was able to provide very satisfactory work conditions, despite demanding work with cancer patients, by ensuring a continuous education program and providing an environment that stimulated the staff's own initiative but was also capable of supporting staff when necessary (32).

Recognizing the economic constraints of the current work environment, all professional groups need to work with administration to develop new roles. In addition, opportunities abound for the development of roles in a variety of settings (117).

Educational Interventions

The work of Florio et al. (59) on the work-related stress concept map suggested that specific interventions can be designed and implemented to target specific stress dimensions. They suggest, for example, that skills training in conflict resolution and assertiveness might be more helpful for oncology nurses in dealing with stressful interactions with physician contacts and less helpful when dealing with patient and family suffering. They suggest interventions for oncology nurses including skills training, relaxation training, job redesign, support groups, and policy changes.

Training in management skills appears to reduce the stress of overload and increase professional esteem. Equipping clinicians with these skills should increase personal competence in meeting the demands of the job and reduce levels of burnout and psychiatric disorder (30). Dealing with patients and families was generally seen as being the most important source of work satisfaction. Communication skills training has been suggested to reduce stress and enhance the satisfaction of dealing with patients, as well as reducing the stress of dealing with treatment toxicity and errors, and enhancing professional self-esteem (30). An educational and supportive intervention program showed that it was possible to reduce burnout in medical oncology house staff at MSKCC (28,118). Furthermore, the patients on the intervention unit perceived the house staff as being more empathic, sensitive, and compassionate.

CONCLUSIONS

The evidence shows that the stress and burnout caregivers experience continues to be an important issue among those engaged in palliative care. The evidence indicates that this may be increasing, especially in oncology. Clearly there is stress associated with the empathic relationship with patients and families, particularly those approaching death. However, much of the stress experienced by caregivers continues to come from the work environment. The increasing workload that is occurring due to the aging of the population, the aging of the nursing workforce, and the economic constraints imposed by health care changes (e.g., managed care) are significant issues that need to be addressed to provide the care that is needed by the vulnerable members of society.

Evidence from the United Kingdom has shown the greater risk of burnout in clinical oncologists whose work-loads are on average two and one half times that of their colleagues in major European countries and the United States (30). Additional evidence of stress in oncologists in Ontario, whose workloads have also significantly increased, also lends credence to concerns about burnout and work-load. To date, most studies have dealt with the perception of work overload that caregivers report, and have not attempted to document the actual work being performed. Future research needs to determine at what point increasing workloads jeopardize patient care, caregiver health, and home life. The evidence has shown that younger caregivers may be at particular risk of burnout. Programs to target this group have been shown to be effective (118), but more evaluation studies are needed. Further work on personality hardiness as a buffer in the work environment is also indi-cated. Perhaps those with hardy personalities and the ability to exert control in the work environment will have a role to play in helping to determine realistic expectations in the work setting.

With the current economic climate necessitating signifi-cant changes in models of care delivery, it is important to continue to assess the stress of oncology practitioners over the coming years to assure that optimal patient/family care is provided by practitioners who recognize the need to care for themselves to be able to care for patients within organi-zations that provide the necessary administrative support needed for a healthy organization with realistic workloads.

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62

ASSESSMENT OF DECISION-MAKING CAPACITY

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In the practice of palliative care, patients face many important decisions. These decisions range from determining which possibly curative treatments to choose from among a range of available options to determining the appropriate point to forgo attempts at curative or life-sustaining treatment. These health care decisions are among the most important not only for the patient, but also for the patient's family and loved ones. At some point in the disease process, many oncology patients lose the capacity to make these decisions, yet these decisions need to be made. If the patient is unable to make these decisions, others will need to make them. If the patient has planned wisely, the decision will be made by an individual whom the patient trusts and who understands the patient's health care preferences. If not, those decisions will be made by others, who may not have any idea what the patient would have wanted.

When patients can no longer make health care decisions, they lose the ability to exercise a fundamental liberty, the right to self-determination. Additionally, the burden of making those choices then falls on the health care team and others, most often family members. Understanding the concept of decision-making capacity and determining whether a patient has decision-making capacity is important for another related reason. If the patient has executed an advance directive, this right to make health care choices may be exercised through a living will, the appointed agent, or a surrogate. The absence of decision-making capacity is the trigger for the activation of an advance directive (1). When there is no advance directive, many states have statutes that allow for automatic appointment of a surrogate. A patient's lack of decision-making capacity triggers the appointment of a surrogate decision maker (2). Thus, a determination that a patient is nondecisional has important legal, ethical, and social implications.

BASIS FOR MAKING HEALTH CARE DECISIONS: INFORMED CONSENT

Informed consent is a necessary component of the process of shared decision making between doctor and patient (3). Informed consent is also a central and fundamental tenet of bioethics and American law. The legal evolution of informed consent, based on the right to determine what shall be done with one's own body (4), began early in this century. It has been expanded to encompass the requirement that consent for medical procedures be informed with disclosure of risks (5). In some states, the risks disclosed should be those considered material by the reasonable person, rather than those that a professional might consider adequate (6). Informed consent encompasses the possibility that the patient may refuse the proposed intervention. The patient's legal right to refuse life-sustaining medical treatment is grounded in commonlaw respect for bodily integrity. The patient's liberty interest is protected by the Due Process clause of the Fourteenth Amendment of the Constitution. The most important expression of this principle was enunciated by the U.S. Supreme Court in the Cruzan case, in which the question, in part, was whether an individual has a constitutional right to refuse treatment (7). Other courts have affirmed this principle, which applies even in cases in which the patient does not have a terminal illness (8,9).

Refusals of proposed treatments must also be informed. Physicians must disclose information about the consequences of the refusal (10). Patients who are not decisional do not lose their rights to self-determination. Rights of nondecisional patients may be exercised by authorized surrogate decision-makers, such as an agent designated by a power of attorney for health care.

The basic elements of informed consent are as follows: (a) The patient's physician must disclose information appropriate to the decision (i.e., risks and benefits, alternative therapies, no treatment); (b) the patient must have the capacity to make health care decisions; and (c) the patient's decision must be voluntary, with a lack of coercion or undue influence by others on the patient while making the decision (11).

In palliative care, in which patients are facing the end of life, informed consent is important for two reasons beyond the fact that it is a basic legal and ethical requirement for all medical interventions. First, many patients and families who are facing treatment withdrawal may have not been fully informed of the risks and benefits of the therapy at the time it was begun. They may not have been told that treatment would be withdrawn if it was no longer effective. After being fully informed of the burdens of continued treatment, the patient or surrogate may elect to stop.

Second, patients and families who refuse further treatment should be told the consequences of the discontinuation of the treatment, just as they are informed of the benefits and risks of other interventions.

However, there are two circumstances in which informed consent may not be required. In an emergency, physicians are able to treat patients without obtaining consent under the *emergency privilege*, a legal exception to the requirements of informed consent. Emergency privilege requirements are as follows: (a) The patient must be unconscious, or without the capacity to make a decision, while no one legally authorized to act as agent for the patient is available; (b) time must be of the essence, in the sense that there is a risk of serious bodily injury or death; and (c) under the circumstances, a reasonable person would consent (12). However, this emergency exception does not pertain if the patient has decision-making capacity and is able to communicate his or her decision about medical care, or if the patient has authorized someone to speak for him or her, and that person is available to represent the patient's interests.

There is another rarely used exception to the requirement of informed consent known as *therapeutic privilege*. Under this exception, if a patient would become so emotionally ill or distraught on disclosure of information so as to foreclose a rational decision or pose psychological damage to the patient, the physician is not required to disclose the information. This therapeutic exception has been used extremely rarely and courts are careful to circumscribe the physician's privilege to withhold information for therapeutic reasons for fear that the exception might devour the duty to disclose entirely (13). Absent an emergency without a surrogate, or the rare circumstances of the therapeutic exception, the physician is required to obtain informed consent for testing and treatment.

DECISION-MAKING CAPACITY AND CONSENT

Central to the concept of informed consent is that patients who have the capacity to make medical decisions may accept or refuse treatment, even in circumstances in which the majority of reasonable persons would not make a similar choice, as long as the patient understands the implications of the choice (14). Thus, a determination of a patient's decision-making capacity is crucial to the patient's ability to make an autonomous choice and, in some cases, the patient's ability to exercise the right to refuse treatment.

In each instance that requires patient consent, health care providers must consider the patient's capacity to give consent. Not every medical encounter requires a formal determination of a patient's decision-making capacity. In fact, practitioners often assume the patient has decisionmaking capacity unless there are signs to the contrary. Questions of patient capacity in decision making typically arise only when a patient chooses a course other than the one the health professional finds most reasonable—often a refusal of treatment (15). However, in all medical encounters health care providers are making *some* judgment of this capacity, even if only by observing the patient and evaluating the appropriateness of the patient's responses to questions. For those encounters in which decision-making capacity is at issue, a formal judgment should be made. Physicians taking care of patients at the end of life should consider the patient's decision-making capacity before presenting the

patient with significant health care decisions.

DETERMINATION OF DECISION-MAKING CAPACITY

A court of law may determine a patient to be incompetent and appoint a guardian to make important decisions for the patient, including those concerning health care. However, many patients who have not been declared incompetent by a court nonetheless have problems with their ability to make health care decisions. Clinicians are often faced with patients who have never been declared incompetent by a court, and either have questionable decision-making capacity or, as in the case of the comatose patient, have no decision-making capacity at all.

Although courts routinely determine a patient to be incompetent based on the expert opinion of a physician or psychologist, appellate courts have rarely scrutinized the process or standards for determining decision-making capacity. Thus, the elements of decision-making capacity have been best delineated by health care professionals and ethicists rather than the courts. One formulation, based on the analysis of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (the Commission), is well recognized and is useful in clinical practice (16). Another analysis of decisionmaking capacity recognizes five increasing standards, including the ability to communicate a choice, the ability to make a reasonable choice, the ability to appreciate the circumstances of the decision, the ability to reason to consider consequences and compare them, and the ability to understand and paraphrase the meaning of the information disclosed (17). Each of these recognizes important elements of the patient's capacity to make medical decisions.

Elements

Simply put, in assessing a patient's ability to make a decision regarding health care, one must evaluate three elements of the capacity to make health care decisions. First, the patient must possess the ability to comprehend the information about the medical problem and to appreciate the impact of the disease and the consequences of various options for treatment, including forgoing treatment. Second, the patient must possess the ability to evaluate the options by comparing the risks and benefits of each option, to deliberate in accord with his or her own values, and to make choices that are not irrational. The patient should also be able to maintain a consistent choice over time. Third, the patient should be able to communicate his or her choice (18). A useful mnemonic for these elements of decision-making capacity may be to analogize the processes to those performed by a computer, with its ability to take in information, analyze it against an internal set of values, make a decision, and communicate it. Any break in the chain of processes may constitute a lack of decision-making capacity. Of course, the analogy is imperfect because a human being's thought processes are significantly more complex and nuanced than a computer's, and may be affected by important values besides logical analysis. Values may change over time or after consultation with physicians, family, and friends (Table 62-1).

TABLE 62-1. EVALUATING DECISION-MAKING CAPACITY

Each of these three basic elements of decision-making capacity can be delineated further. First, the patient must possess of a set of values and goals, including a framework for comparing options, and the ability to make reasonably consistent choices. Second, the patient must have the ability to communicate and to understand information, including the ability to give and receive information; the possession of linguistic and conceptual skills needed for at least a basic understanding of the relevant information; and sufficient life experience to appreciate the meaning of potential alternatives. Third, the patient must have the ability to reason and to deliberate about choices, including the ability to compare the impact of alternative outcomes on personal goals and life plans, some ability to employ probabilistic reasoning about uncertain outcomes, and the ability to give appropriate weight in a present decision to various future outcomes (19).

This analysis may at first look to be a daunting standard by which to be measured even for those who have full decision-making capacity. However, the Commission recommended that the measurement of decisional capacity not be absolute, but rather measured by a “sliding scale.” Generally, determination of the capacity to decide on a course of treatment must relate to the individual abilities of the patient, the requirements of the task at hand, and the consequences likely to flow from the decision. Thus, when the consequences for well-being are substantial, there is a greater need to be certain that the patient possesses the necessary level of capacity (20). When a decision to forgo treatment could result in death, the need to be certain that the patient has decision-making capacity is greatest.

A lack of decision-making capacity may be caused by any break in the chain of decision making: the ability to understand, to reason and evaluate, or to communicate a decision. Obviously, patients in a coma, infants, and the profoundly mentally disabled lack decision-making capacity for all medical decisions. Some other patients, such as those at the end of life who have metabolic abnormalities, disorientation, or early dementia, although impaired to a certain extent, may yet retain some degree of decision-making capacity.

Thus, decision-making capacity has two seemingly contrary characteristics. Decision-making capacity has characteristics of a continuum (21) (i.e., a sliding scale that relates to the complexity, importance, and consequences of the decision in relation to the patient's abilities)—the more grave the decision, the higher the standard. Yet in the final analysis, at a given point in time, for a given patient with a specific health care decision to make, it is all or nothing: A patient either has the capacity to make a specific health care decision or does not.

Role of Mental Status Examinations

A mental status examination may be a useful tool in determining decision-making capacity. A commonly administered test is either the Mini-Mental State Examination or a variation of it. The Mini-Mental State Examination establishes orientation, memory, attention, and reasoning ability through the use of vocal responses. It also tests the ability to name objects, to follow verbal and written commands, to write a sentence spontaneously, and to copy a complex polygon (22). This short test is foundational for demonstrating a normal mental status, but may not address some of the critical issues of determining decision-making capacity, e.g., understanding nature, risks, benefits, alternatives, and consequences.

For the mentally impaired by developmental disability and the elderly, there are other brief measurements of cognitive functioning, including the Dementia Rating Scale and the Alzheimer's Disease Rating Scale (23). There are also tests for the possibility of intercurrent depression, as well as tests for social function, including subjective well-being and coping skills (24). None of these is designed to measure the specific elements of decisional capacity, although they may be contributory to the overall evaluation.

There should also be a realization that a strict standard of comprehension of information does not reflect the reality of informed consent in the general population. Studies of the ability of persons with normal cognitive abilities show that patients often cannot comprehend or remember the information they are given during the discussion of a procedure and its benefits and risks (25,26). Additionally, because informed consent may evolve in relation or reaction to a new medical condition or situation, it should not be expected that patients will have perfect comprehension of the risks, benefits, and alternatives and that they will be ready to make an immediate decision without some reflection, consultation, and perhaps, vacillation.

Who Should Determine Decision-Making Capacity?

Clinicians already use a rough measure of decision-making capacity when examining or speaking with a patient. Most determinations of decision-making capacity do not rely on special expertise. Psychiatric or psychological consultation may be helpful for some difficult situations in which depression or mental illness may cloud judgment and might be treated. Additionally, mental health professionals have special expertise in analyzing patient thought processes. However, in most cases, any clinician should be able to determine decision-making capacity in a formal way using the standards described in the section Determination of Decision-Making Capacity.

Decision-Making Capacity and the Legal Consensus on Withdrawal of Life-Sustaining Medical Treatment

In the past two decades, federal and state courts have decided a number of cases that have established a consensus of important legal principles in end-of-life care. The first principle is that patients with decision-making capacity may refuse unwanted medical treatment, even if this could result in their death. This principle was stated by the U.S. Supreme Court in the Cruzan (27) case, in which the court recognized that an individual has a constitutional right to refuse treatment (in this case, nutrition and hydration for a patient in a persistent vegetative state). The court grounded this in both the common-law respect for bodily integrity and the liberty interest articulated in the Fourteenth Amendment to the Constitution (28). The second principle is that patients who lack the capacity to make medical decisions do not lose

their rights to refuse life-sustaining medical treatment. However, the manner in which these rights may be exercised is different. Authorized surrogate decision makers may make decisions to limit treatment for patients who lack decision-making capacity using standards discussed in the section Implementing the Patient's Wishes: Standards. The third principle is that courts have recognized that withholding or withdrawing lifesustaining medical treatment is considered neither homicide nor suicide. The fourth principle is that courts have drawn a distinction between intentionally causing a patient's death, which remains illegal, and allowing a patient to die as a result of the withdrawal of life-sustaining medical treatment, which is permitted under appropriate circumstances (29).

Thus, because patients have the right to refuse lifesustaining medical treatment, the determination of decisionmaking capacity can be a life-or-death key to differentiating between a legitimate refusal of treatment by a patient with the ability to evaluate the options, understand the implications, and communicate a choice that should be respected, and a refusal by a patient who no longer has this capability and whose refusal in some cases may be overridden.

SPECIAL POPULATIONS

Minors

By legal definition, minors (those younger than 18 years of age) may not make health care decisions. There are statutory exceptions for some specific medical problems— contraception, sexually transmitted diseases, and substance abuse, among others. However, minors can reach a status where they may be considered to be emancipated or mature for medical decision making; this may be determined by statutory recognition (e.g., those minors who are living independently, enrolled in the armed services, or are married) or by a court that determines that an individual minor is legally capable of making a medical decision. Bright line rules aside, adolescent minors who are undergoing supportive oncological care and who exhibit the essential elements of decision-making capacity should be given great latitude by parents and clinicians in medical decision making.

Patients with Dementia and Psychiatric Disorders

Because mental disorders such as delirium or dementia are common reasons that patients lack decision-making capacity, the presence of a psychiatric disorder should alert the clinician to take special care in determining decision-making capacity. Patients with delirium are rarely able to make health care decisions because of the inability to concentrate. Patients with dementia may be unable to make medical decisions because of cerebral frontal lobe impairments that affect abilities such as memory, insight, and judgment. However, a diagnosis of dementia alone is not sufficient to determine lack of decisionmaking capacity (30). Even the person with somewhat advanced dementia may have intermittent periods of lucidity that allow for significant decision making. As an example, some patients may be relatively lucid in the early hours of the day, but grow more confused as they tire. Presumably, because there is a consistent period of lucidity, this type of individual could still participate in decision making about medical care.

In addition, patients with psychiatric disorders such as schizophrenia may have diminished decision-making capacity due to delusions, denial of illness, or impairments in memory and concentration. Although approximately one-half of patients with schizophrenia have impaired decision-making capacity, another half may be able to make medical decisions (31).

It is also important to note that the presence of depression does not automatically interfere with decision making. Depression is a natural and rational response to cancer, and the depression may be ameliorated by antidepressants. The key question is the degree to which the depression affects the processes of decision making.

PROBLEMS IN THE DETERMINATION OF DECISION-MAKING CAPACITY

Vexing Problems in Determining Decision-Making Capacity

The Commission and others have cautioned against using the objective outcome of a decision process as a test of whether a patient lacks decision-making capacity (known as the *objectively correct standard*). Thus, just because the decision seems wrong or against recommendations does not mean that the patient who made it does not have decision-making capacity. Conversely, the Commission also recommends against using the patient's concurrence with recommendations as a similar test. Intuitive thought processes and feelings may lead patients to make medical decisions that seem to be wrong, or at the least, suboptimal (32). Physicians and others may deem these decisions irrational, retrospectively categorizing the patient's decision-making capacity as flawed (33).

It has been said that few problems in medical ethics are as intractable as that of patient decision-making capacity (34). In the most difficult cases, a patient may make a medical decision on reasoning that is not logical, but rather is based on intuition and feelings. Such decision making is not so foreign in other venues (e.g., refusing to board an airliner for a trip due to fear of flying, while being willing to drive the same distance without wearing a seat belt—a statistically far more dangerous choice), but when the refusal of what may be life-sustaining medical treatment does not seem to be based on a logical conclusion of a patient's expressed values, clinicians are understandably perplexed.

The few courts that have wrestled with these most difficult cases have found the patient to be incompetent when the patient is “incapable of recognizing facts which would be obvious to a person of normal perception,” such as the refusal to recognize a malady and its consequences (35). On the other hand, a patient with an abnormal mental status has been allowed to refuse treatment as long as the patient understood the nature and severity of illness, despite the fact that recovery without treatment was extremely unlikely, and treatment was almost uniformly effective (36).

Patients also make important health care decisions based on religious beliefs that may not be commonly accepted. The Constitution's First Amendment protects religious belief and practice from government interference, but unless the hospital is a government entity, the First Amendment would not apply as a bar to treating patients against their wishes when their refusal is based on religious grounds. However, appellate court precedent allowing a physician to override an adult patient's religious refusals of treatment (37) has given way to precedent that respects such refusals as competent (38). A patient's hope for a miracle while refusing indicated treatment does not automatically indicate a lack of decision-making capacity (39).

Pearls and Pitfalls in the Determination of Decision-Making Capacity

A recent survey of clinicians culled and ranked a number of common pitfalls in the determination of decisionmaking capacity (40). They encompass the most common misconceptions:

1. Legal competency is not synonymous with medical decision-making capacity. Legal competency, as determined by judicial proceeding, differs from clinical determination of decision-making capacity. Clinicians should be able to determine a patient's medical decision-making capacity.
2. Capacity is not all or nothing for all medical decisions, as individuals may have the capacity to make some decisions but not others.
3. A patient's capacity to make a particular medical decision is not static. It may change over time, caused by fluctuations in mental status.
4. The fact that a patient is able to communicate a decision does not necessarily mean that the patient has decisionmaking capacity. When assessing capacity, the clinician should give more weight to the process a patient uses to make a decision than to the final decision itself.
5. A clinician's agreement with a decision made by a patient does not necessarily indicate that the patient has decision-making capacity. The clinician should still assess a patient's decision-making capacity even when the patient agrees with the clinician's recommendations.
6. Patients who are given inadequate information may have the capacity to make a decision, but the clinician should ensure that the patient has been given relevant and consistent information about the proposed treatment so that the patient can make an informed decision.
7. Patients should not have to bear the brunt of decision making alone. The clinician should take steps to optimize the patient's capacity to make decisions, including time to make decisions, careful phrasing, teaching aides, use of personnel specially trained to bridge language and cultural barriers, and, where the patient permits, the enlistment of family members to help with communication.
8. Just because a patient has a psychiatric diagnosis does not mean that the patient automatically cannot make health care decisions. Patients with psychiatric disorders may still have the capacity to make medical decisions. Patients with schizophrenia and early dementia, for example, may have the ability to make medical decisions.
9. The fact that a patient is committed to a mental health institution does not mean that the patient cannot make health care decisions. Even patients who are committed to a mental health institution may retain the right to make health care decisions.
10. In most cases, mental health professionals are not necessary to determine a patient's capacity to make medical decisions. Clinicians of all stripes should be able to make a determination of patients' decision-making capacity, although mental health expertise may be helpful for the more difficult cases.

DECIDING FOR PATIENTS WITHOUT DECISION-MAKING CAPACITY

Legal Devices for Making Health Care Decisions

Once a patient has been found not to have decisionmaking capacity, how should medical decisions be made? Traditionally, if no other provisions have been made by the patient, the legal standard for making both medical and nonmedical decisions for patients determined by a court as incompetent has been to establish a guardianship. The guardianship process is often slow and costly for the patient or family, and the guardian is normally expected to make decisions using the traditional “best interest” standard, which does not always rely on the patient's previous expressions of preferences. In practice, in the interim before a guardian is appointed, clinicians have informally turned to a spouse or family member (one of whom would most likely be appointed guardian) for decision making. Even with a guardianship, withdrawal of life-sustaining medical treatment poses special problems in determining what a patient would have wanted under the circumstances. Advance directives were created to address these problems.

Advance directives give legal recognition to the previously expressed desires of the now incapacitated patient. Advance directives, which consist of directives for medical care made in advance of incapacity, act as expressions of patient wishes for the now nondecisional patient. Advance directives were recognized and encouraged in the Cruzan case and the Federal Patient Self Determination Act that followed it (41). As a result of the Patient Self Determination Act, each state must recognize at least one form of advance directive and hospitals are required to inform patients of their right to refuse medical treatment and to make advance directives. The two most common forms of advance directives are the living will and the power of attorney for health care. The living will is a document that directs physicians to withhold life-sustaining medical treatment if the patient is nondecisional and has a terminal illness (or, in many states, is in a persistent vegetative state). The power of attorney for health care is a document that appoints an agent to make health care decisions for the patient when the patient becomes incapacitated. Both documents are triggered when two physicians (or a physician and a psychologist) determine that the patient no longer has decision-making capacity for the health care decision at hand. Advance directives give immunity to physicians who follow the directive in good faith.

Despite the availability of these documents, the majority of individuals do not complete advance directives. As a result, a number of states have enacted surrogacy laws (42). Under a surrogacy law, patients without advance directives who become incapacitated may have a decision-maker appointed from a list of eligible individuals, including a spouse, family member, or others as prescribed by statute. Surrogacy laws give legal recognition to a process that many physicians have turned to in the past when no one had been appointed as guardian, namely, turning to the person most likely to be recognized as the appropriate representative of the patient (43).

However, until greater numbers of patients complete advance directives, doctors, family members, and others are faced with the task of making decisions about limitation of treatment without these legally approved expressions of patient preference in the majority of end-of-life decisionmaking cases in which patients do not have decision-making capacity. This task generally includes a process of either acting in what is perceived to be the patient's best interest, or, where state law permits, acting according to the previously expressed preferences of the patient.

Implementing the Patient's Wishes: Standards

Decisions to forgo life-sustaining medical treatment in the patient who no longer has decision-making capacity have been the subject of scrutiny by the U.S. Supreme Court and numerous state courts and legislatures. For nondecisional patients, state courts, for the most part, have recognized two criteria to measure whether the now nondecisional patient would forgo life-sustaining medical treatment. One test requires determination that treatment would not be in the “best interest” of the patient. This test is a similar standard to that which a guardian must exert on behalf of his or her ward, or parents on behalf of their child—namely, the patient's wishes aside, what would be best for the patient.

Another test allows a “substituted judgment” to determine what the patient would have wanted under the circumstances to justify treatment termination (44). This test takes into account the patient's subjective wishes. Depending on state law, withholding or withdrawal of life-sustaining medical treatment is permissible when the appropriate test is satisfied. When a patient has not made an advance directive that addresses the medical question at hand, a statepresribed surrogate or others who make decisions for the patient are faced with the task of making those decisions, relying on whatever evidence exists of the patient's wishes regarding end-of-life treatment.

States have different standards for determining the nondecisional patient's prior treatment wishes. When not stated explicitly, it is generally assumed that a preponderance of evidence is required (i.e., it is more likely than not that the patient would have made a particular health care decision). Some states require a higher degree of certainty (“clear and convincing” or “clear” evidence) that the patient would have chosen a particular course of action in health care decision making. The difficulty in relying on previous verbal expressions of the patient's health care preferences reinforces the importance of advance directives in adult end-of-life planning. End-of-life decision making for patients who were never decisional (e.g., adult incompetent patients who never had decision-making capacity) generally requires an individual who is legally able to act in the patient's best interest, such as a guardian.

Quality of life may arise as a factor to consider when deciding when to forgo life-sustaining medical treatment. Physician perception of poor quality of life can influence recommendations to forgo life-sustaining medical treatment (45), even in cases in which concerns about poor quality of life might not be shared by the patient. Physicians tend to underestimate patients' preferences for life-sustaining medical treatment in chronic illnesses, whereas family members may overestimate the patient's preferences in the same circumstances (46). Unless patients have stated in an advance directive or by other means how they would evaluate their present state, quality-of-life considerations in patients who are now nondecisional are extremely problematic. Nonetheless, without an advance directive that incorporates patient wishes, there seems no better choice than to rely on family and loved ones for expressions of patient preference. This reinforces the need for advance directives that appoint a surrogate while still providing important information about patient wishes.

Clinicians facing difficult decisions concerning patients at the end of life may be aided by consultation with their institutional ethics committee or ethics consultant. Health care institutions are mandated by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) to have a mechanism to resolve ethical issues, and most health care institutions have established ethics committees or ethics consultants. The committees or consultants have developed processes to allow clinicians and others, including patients and families, to consult them for advice in resolving difficult ethical issues in patient care. Ethics committee deliberation and ethics consultation can provide a forum for discussing end-of-life decision making and making recommendations regarding ethically appropriate choices in a given situation.

SUMMARY

In the practice of palliative care, patients, their families, and their loved ones face many important decisions. At some point in the disease process, many oncology patients lose the ability to make these decisions, yet treatment decisions still need to be made. The elements of decision-making capacity serve as a standard to determine whether a patient is decisional or not. Mental status examinations may be helpful but not necessarily determinative of incapacity. In most circumstances, clinicians should determine decision-making capacity. Nonetheless, vexing problems arise in determining decision-making capacity that may require mental health expertise. Legal devices for making health care decisions for patients without decision-making capacity include guardianship, advance directives, and surrogacy laws. There are statespecific standards as to the test to be applied in deciding what a patient would have wanted under the circumstances. Ethics committee and consultants may be helpful in difficult cases.

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ADVANCE DIRECTIVES

LINDA L. EMANUEL

Many oncology patients would like to have some control over their medical care, not only when they are alert but also when they are too sick to participate in decisions. Similarly, those who have to make decisions for patients who are unable to participate would like to be guided by the patient's wishes. Advance care planning evolved in response to these needs. Having discussions about goals in different types of scenarios and including both family and physician in that discourse are the key issues. For effective discussions, it helps to have the patient and family go through validated worksheets that walk them through the various considerations and result in expressions of preference that are clinically meaningful. This should usually be done on the patient and family's own time, with opportunities to check in with the physician and team to ensure coordination and agreement. Ideally, this can happen over time, integrated into the course of care.

TERMS, HISTORY, AND LAW

There are two main modalities by which a person can make preparations in anticipation of future incapacity (1). One is to appoint a proxy to speak in the place of the principal person. The other is to write down wishes in a directive. These two modalities are usually complementary, since written statements cannot provide for all eventualities, and proxy decision-makers cannot speak accurately on behalf of patients without the patient's guidance.

Proxy Designation

Physicians should be aware of three key issues on which to advise patients and proxies. First, patients, professionals, and the proxies themselves should understand the proxy's role. Speaking in place of the patient can take two distinctly different forms. In one form, the patient asks the proxy to represent the patient's prior wishes and to hold steadfast to these known prior preferences, extrapolating them if necessary to the situation at hand. In the other form, the patient simply chooses the proxy and lets him or her speak according to the proxy's own judgment (2). In this alternative role, the proxy remains more independent of the patient's stated prior wishes and tries instead to imagine what the patient would have wanted in the circumstances, judge the best interests of the patient, and balance other issues as he or she sees fit. These two modalities can be merged. For instance, a patient may tell a proxy to apply his or her prior wishes, albeit with latitude and taking particular types of unpredictable family issues into consideration (3).

Second, patients and proxies should know that studies have found that proxies often guess the prior wishes of patients inaccurately and, furthermore, that proxies often imagine that the patients' prior wishes are for more intervention than patients actually select (4). Even a proxy who has had a close relationship with the patient may not be able to make accurate judgments. It is possible that close relationships do not often include discussions about medical aspects of dying, or that patients do not even know their own preferences until they have discussed or faced a relevant matter. It is also possible that proxies face significant emotional issues that may hinder their ability to imagine the patients' wishes. Regardless, physicians must counsel patients to discuss relevant perspectives explicitly and well in advance of a deteriorating medical situation that may result in incompetence.

Third, patients should be aware that friends and family members have their own interests and issues, which may conflict with their role as proxy. Common examples include the difficulty of letting go of the loved patient, the great emotional burden of making life-and-death decisions, the difficulty of finding the extensive time it takes to perform the proxy role well, and the difficulty of choosing how to allocate limited family resources (e.g., to the patient's medical care versus the children's education) (4). Conflicting motivations are inevitable and need not prohibit the proxy role. Nonetheless, the proxy may need help distinguishing different motivations and abiding by those that are most suited to the proxy role.

Instructional Directives

The history of the development of instructional directives reflects the search for the most valid form of expressing prior wishes. The earliest commonly used instructional directive was the “do not resuscitate” (DNR) order, written by the physician after discussion with the patient and family (5). After its proposal in 1976, a set of studies and a culture evolved around the DNR discussion. It is still relevant and can be included in comprehensive advance planning discussions (6). A hazard of isolated DNR discussions is that they occur too late, either missing the patients who need them or occurring in such “out of the blue” conversations that patients get unintended messages, perhaps feeling that they are being abandoned (7).

An earlier modality for making instructional directives, which never achieved widespread use in the medical system, was the living will. This was introduced in 1968 by a lawyer, Louis Kutner. The living will attempted to express the widespread view that heroic levels of technological intervention should be avoided if the patient's prognosis was hopeless. The statements made in living wills were true enough to the sentiment, but in practice they were insufficient to guide the specific decision-making needed in real clinical circumstances. Different interpretations of what constitutes a heroic intervention and what constitutes a hopeless prognosis meant that this early type of living will was liable to bring as much confusion as clarity to the decisions.

Efforts to increase the specificity of living wills began, starting most notably with Sissela Bok's and Michigan's living will (8,9). Thereafter, developments began along two lines: one to better describe the general health-related values of the patient (values histories) and one to formulate ways in which patients could make very specific treatment preference statements (treatment-specific directives) (10,11). Empirical evidence that general statements cannot predict specific wishes has supported the more balanced view that these two modalities work best together (12,13 and 14). Some patients are inclined to write a free-prose letter encapsulating their wishes. Such letters can be worthwhile, but many patients do not have the writing skills or the specialized knowledge that ensures coverage of relevant decisions. In such cases, concurrent use of predrafted documents is to be encouraged.

More recently, efforts have been focused on the need to validate predrafted instructional directives, just as any other instrument that seeks to record subjective matters

needs to be validated (15). Specific forms that have been extensively validated are still few, and validated forms tailored to oncology patients are even fewer. One of the more studied forms, which is generic and adaptable, is reproduced in Appendix 63-1. Physicians should advise patients to use validated forms, since using nonvalidated forms risks misrepresentation of patients' true wishes and can confuse decisionmaking. Validated forms also provide a succinct method of ensuring that patients have considered the major areas that most people need to cover. The use of a validated form as a worksheet for thought and discussion can be as important as its use as a recorded document.

Statutory versus Advisory Documents

All states and the District of Columbia have statutes that endorse advance directives in one way or another. Some endorse the use of proxies, others endorse the use of instructional directives, and most now endorse both (16). Most state statutes have a corresponding document, which is often available from local health care facilities or state medical organizations. The fundamental purpose of state statutes is to allow physicians to follow the patient's wishes without fear of liability. The interests of the patient are served indirectly by protecting physicians who follow patients' wishes and rendering physicians vulnerable if they do not. Many states specifically honor the statutory documents of other states, although some differences exist, and frequent travelers may wish to have documents from their frequented state bound together with those from their home state.

It is part of common law that competent patients have the right to accept or refuse medical intervention, even lifesustaining intervention. Even casual statements have been honored as sufficient evidence, although written statements have been explicitly identified as desirable evidence of patients' preferences (17,18). Physicians can therefore be assured that patients' statements recorded in a fashion not specifically designed for local state statutes—they can be considered advisory documents—still carry legal authority. Distinctions between legal and “nonlegal” or “illegal” forms in this context are erroneous. A statutory form is legally binding, and a nonstatutory advisory document is also binding if it provides clear evidence of the patient's wishes. Since statutory forms are written to comply with legal criteria, they are often far less informative than advisory documents, which can address personal values and clinical issues.

Patient Self-Determination Act and Recommendations of the Joint Commission on Accreditation of Healthcare Organizations

In 1990, the U.S. Congress passed the Patient Self-Determination Act, which requires that patients be asked about the existence of an advance directive at the time of enrollment or admission to a health care facility. The intent of the law was to increase awareness and documentation of advance directives. In addition, the Joint Commission on Accreditation of Healthcare Organizations recommends that facilities have arrangements for counseling patients who wish to complete advance directives. Completion of advance directives is best done in the more stable setting of continuing outpatient care, but occasionally their completion in the inpatient setting is unavoidable. Thus, although minimal compliance with the Patient Self-Determination Act and the recommendations of the Joint Commission require relatively little from physicians, the spirit of both requirements involves thoughtful, longitudinal involvement of the physician in discussion with the patient.

CONCEPTUAL FOUNDATIONS, EMPIRICAL BACKGROUND

Honoring Patients' Wishes

The basic precept on which advance directives depend is somewhat confusing. The notion that autonomy can be extended into times of incompetence by recording wishes ahead of time is problematic. How can anyone know whether the wishes of an incompetent person are represented by previously recorded wishes? What about patients who are incompetent for decision-making but are awake and appear to be capable of feelings and wishes, and these apparent wishes differ from the prior wishes? Responding to these two questions, which motivated considerable criticism of the advance directive movement, depends on understanding two things. First, the justifying principle for advance directives is surviving interests, rather than the broader principle of autonomy. Second, the patient condition in which advance directives pertain is actually wishlessness, not the more general condition of incompetence (19).

Surviving Interests

Ordinarily, autonomy involves application of real-time wishes. But since it is impossible to create real-time wishes when there are none, autonomy can be extended only by applying prior wishes. A surviving interest constitutes a distinct form of autonomy and should not be confused with the more general autonomy. *Surviving interest*, ordinarily a legal term, refers to the right of the individual to determine decisions on matters in which he or she has an overriding interest even after losing the direct ability to act on these matters. The most common example is the estate will, in which individuals exercise their right to determine disposal of their property after death. A related arrangement that relies on a surviving interest concerns the funeral directions by the principal planning for his or her own death. Another example is the organ donor card. The important point is that arrangements predicated on surviving interests do not rely on real-time wishes; they rely on prior wishes. Advance directives rely on prior wishes in just the same way as these more traditional applications of surviving interests. Even when a proxy is instructed to make decisions without reference to the patient's prior wishes, the proxy's authority relies on the patient's prior wishes to designate him or her, and while proxies may make use of their own real-time judgments, there is no application of the patients' (nonexistent) real-time wishes. The question, “How can anyone know if the wishes of the incompetent patient are represented by the recorded wishes?” can now be answered— When there are no real-time wishes, it is prior wishes that must be represented.

Zone between Incompetence and Wishlessness

Patients who are in a state in which it is not possible to have wishes, such as occurs when there is complete absence of neocortical function, clearly meet the criteria by which advance directives can be activated. A problem arises when a patient is not wishless but is decisionally incapacitated, as is commonly the case after a stroke or in many types of dementia or debilitated states. Many such circumstances involve such a significant change in patients' personality or states of being that they are very different from the former selves who made out the directive. There is limited ethical imperative to apply the wishes of the former person to the current person if the latter is a significantly altered or truncated version of the former (20). Many patients fall into this “twilight zone,” and advance directives should be used as no more than one factor (the representation of prior wishes of the former person) in the assessment of what the current person's wishes and needs may be. Under these circumstances, advance directives may be said to represent a weak version of the surviving interests of the patients, and other factors must therefore be considered. Technical and legal statements as to when advance directives can be activated often fail to make this distinction. Nonetheless, physicians should be particularly careful to meet ethical standards as well as legal ones under these circumstances. The question, “How should one represent decisionally incapacitated patients who seem to have wishes that differ from the recorded wishes?” can now be answered—A combination of guidance by the advance directive and substituted or best interests judgment should determine the physicians' and proxies' decisions for patients in this circumstance.

Substituted Judgment and Best Interests Judgment

Whenever patients' surviving interests are unknown, decisions must be made by using standards of substituted judgment or best interests judgment. The application of prior wishes is not the same thing as using substituted judgment. Even when prior wishes are inferred from stated wishes to fit unpredicted decisions, this is a form of prior-preference– guided judgment that is justified by surviving interests.

Substituted judgment usually refers to attempts to judge as the patient would have if he or she could have. In the words of Justice Hughes, who wrote the opinion for Karen. Quinlan's case, “If Karen were herself miraculously lucid for an interval (not altering the existing prognosis of the condition to which she would soon return) and perceptive of her ... condition, she [would] decide upon ... [the decision of the court offered on her behalf]” (21). Substituted judgment is an intrinsically difficult concept and is just as difficult to implement in reality. Understanding what a person would want is hard enough in ordinary circumstances. Understanding what a person would want when the person is in a state that the proxy has never been in is even harder. When that state is such that the individual is incapable of having wishes, it is impossible. This last key difficulty centers on the fact that real-time wishes are being created when there are none. Commentators have noted that substituted judgment usually ends up being a version of best interests judgment. It may also end up being a version of priorpreference–guided judgment in that attempts are made to guess what the prior healthy person would have wanted if he or she could have anticipated the eventual condition.

Best interests judgment is somewhat easier conceptually, but still difficult to implement. The idea is to judge according to the best interests of the patient. It has this advantage: Not only is real time used, but also there need be no reliance on notions of the patient's wishes. The difficulty for this concept is determining what the best interests of the patient are, since this involves highly subjective value assessments. It may also be the case that the patient is so debilitated and “absent” that ordinary real-time interests do not exist. Despite these difficulties, it is the best guiding standard available when prior preferences cannot be used.

AUTHENTICITY OF WISHES

Cultural Differences

Advance care planning has evolved in the contexts of Western cultures and is often thought of in terms suited to social contexts in which individuals' rights have some priority. However, the idea of planning is not predicated on individualism and readily accomplished in cultures that emphasize extended families and community

responsibility. Other cultural differences can also invite special consideration, but, similarly, can usually be overcome. When the role of deciding for others traditionally falls to a particular role or person in a culture, it can be that advance planning may seem a threat to that role. Or, if there is distrust of those who seek to plan by those who will be affected, then planning may be counterproductive unless trustworthiness is established. But, perhaps the most problematic cultural issues has to do with cultural prohibitions against discussing dying. This taboo has been as strong in the Western cultures as elsewhere. Delegated decision making to family heads has been identified in families of Asian origins; trust concerns have been identified in African-American patients and families; and concerns over precipitating undesired outcomes if they are discussed has been identified among Navaho families (22,23 and 24). While cultural issues are powerful, generalizations are also problematic. Every case must be engaged on its own issues. The clinician who approaches people with genuine respect and, with an open mind, inquires about and honors cultural differences, should be able to accomplish advance care planning in forms that suit each case and setting. Three practical tips can help with many situations: If extended family decision-making may be desired, ask the patient how he or she would like decisions managed and include the relevant people in the process, perhaps suggesting designation of the decision-maker in the family as the proxy. If trust may be insufficient, spend longer establishing trustworthiness by explaining the nature of your thinking as a clinician, by including other members of the family or community and by avoiding arrogation of decision making and sharing information fully and carefully. If death is difficult to talk about, be extra sure that you are comfortable with the topic and approach it with simplicity and a listening disposition. Ask if there are ways of talking about dying that might be easier and try to accommodate any requests.

Informed Consent and Competence Standards for Advance Directives

Patients' prior wishes are articulated in real time and must be held to the same standards as any other real-time decisions, namely, to ordinary standards of informed consent. Informed consent has received considerable attention, and its standards can be read about elsewhere (25,26 and 27). Although standards may evolve, for the present, physicians should ensure that patients understand the nature of the decision, understand the alternatives, and understand the risks (common or serious) and benefits. Patients should be over 18 years of age, have decision-making capacity in the relevant areas, and give evidence of having made actual active decisions.

Informed consent specifically for advance directives can be considered in two parts. First, patients must consent to completing an advance directive. Patients must know what the basic procedures are (to discuss the issues and record preferences) and understand that traditional decision making (having physicians and legal next of kin use their best judgment) is the alternative. They must know that there are risks either way (e.g., careless advance directives can lead to unintended actions, but traditional decision making is known to correspond poorly to patients' wishes). To be competent in the use of instructional directives, patients have to be competent in the use of imagined scenarios. Otherwise, they will not be able to understand the intervention choices they are making for future potential situations. This is not as dissimilar as it may initially seem from real-time decisions, since real-time decisions are also based on how people think they will feel in the future while living with the consequences of the immediate decision.

Second, discussions of advance directives need to ensure adequate informed consent for any specific treatment decisions made. This can be difficult because of the large number of decisions included in some instructional directives and because of the sketchy nature of delineated scenarios in the advance directive. Many instructional directives specifically state that they are to be used as a guide to the patient's wishes rather than as a series of treatment decisions. For this reason, standards of informed consent can be relaxed to some degree. Nonetheless, the standards must be sufficient to provide an accurate picture of the patient's wishes. The use of well-designed brochures or other information packets that describe key interventions can help ensure informed consent standards. The key interventions should include mechanical respiration, resuscitation, chemotherapy or radiation therapy, dialysis, simple diagnostic tests, and pain control (including the potential side effect of respiratory depression). Whether or not information aids are used, physicians must ensure evidence of patients' comprehension.

Valid Expressions

The validity of prior preferences can be judged in essentially the same way that the validity of real-time wishes is judged. Validation of predrafted instruments for the articulation of subjective matters is a well-developed discipline in itself. Generally speaking, instruments must meet standards of content validity, construct validity, criterion-related validity, and test-retest reliability. The first requires that the instrument cover the relevant content matter, the second that items in the instrument be constructed to fit the concepts of the subject matter, the third that the items bear sensible relationships to existing relevant scales and to one another, and the fourth that if the same items were used over again at a different time a reasonably similar set of responses would be obtained (15). Predrafted advance directives should meet these standards, as adapted to the needs of advance directives (19).

An efficient way for physicians to assist patients in valid expressions and recordings of prior preferences is to provide them with a validated, predrafted, instructional directive and go through it. If patients have been able to complete such a directive, meeting standards of informed consent for the wishes they express, then the statements recorded must be considered valid.

HOW TO DO IT

Five Steps in a Continuing Process

The creation of recorded advance directives is one step in a longitudinal process that should be integrated into the totality of clinical care. Although five steps can be identified, they will rarely be so distinct in actual practice. First is raising the topic. Second, and most important, is structuring a core discussion to cover the main issues and start the patient thinking about his or her views. Third is reviewing the final document and putting it in the medical record. Fourth is updating the directive from time to time. Fifth is ensuring its availability and use, applying it to decisions that arise after the patient has become wishless (28).

Raising the Topic, Providing Background Information, and Advising on Proxy Choice

First, the topic must be raised. This may be the hardest part, although once expected and routinized, it is a surprisingly easy matter.

With whom should the topic be raised? Among oncology patients, everyone should have the opportunity for advance care planning, whether the prognosis for cure is excellent or poor. Occasionally, patients will have discussed advance care planning with their primary care or other physician. The oncologist can build on this foundation. The topic should not be avoided on the assumption that it has been dealt with. Patients who have completed advance care planning before receiving their oncologic diagnosis may have since changed their perspective. The extent and structure of the planning may not have been as good as that the oncologist can offer. Most important of all, the oncologist needs to know the substance of the patient's current health advance care planning.

In an oncology or a palliative care practice, the topic can be raised by the fourth or fifth visit, depending on the emotional and medical circumstances. Time should be allowed before advance care planning for confirmation of the diagnosis, exploration of treatment options, establishment of a solid therapeutic relationship, and some adjustment by the patient to his or her diagnosis. Earlier mention, say at the second or third visit, that advance planning will be a component of routine care (as should occur for all patients with or without cancer) can facilitate the process. In a long-term care facility, an analogous process is possible, with early mention that the discussion will occur, within the first 3 months of a patient's residency.

One fashion in which the topic can be raised is as follows:

> Ms/r. X, I want to talk with you about planning for future medical care. Many now recommend that people make plans whether or not they have an illness, and that doctors discuss these issues routinely with patients. There is even a federal law that aims to let people know that advance planning is available to all people. We should go through these issues together. It is part of getting to know your values and helping to ensure that you are cared for the way you would want to be even in times of life-threatening illness when communication may be impossible. There is nothing new about your health, and I am not hiding bad news that we have not already discussed; planning for the future simply is prudent. Is this something you have explored before?

It is helpful to be able to add, as is true for many oncologists:

> I myself have done this as a routine matter, despite being in good health.

Some issues for the patient to consider in selecting a proxy can be included at this point, in particular that being a proxy is a complex and burdensome task, and that family members and close friends may have interests that conflict with the patient's. Most people prefer to select someone close to them as a proxy nonetheless, and usually for good reason, but the possibilities of appointing a more distant friend or a professional, such as a social worker or lawyer, are worth considering. Some patients suggest appointing the physician as proxy. Since the idea of a proxy is to have someone to talk with the physician, this is not usually the best idea. The patient should be reassured that the physician will in any case be working to make the best decision for the patient and additional proxy powers are usually unnecessary; participation by the physician in creating a written directive, perhaps without a designated proxy, assists the aspiration.

Nonphysician health care providers can assist in the first step of raising the topic and providing background information. Brochures and predrafted forms and videos or

closed-circuit television programs can also be made available in patient information libraries and patient rooms.

Structured Discussion

Second, the topic must be discussed. This is usually done best by the patient and family on their own time, once they have been oriented to key features of the task. The proxy should be present at this discussion whenever possible. He or she can be advised to listen and ask for any needed clarification, in preparation for the potential role of speaking for the patient, and may even act as scribe, penciling down the patient's statements.

The most efficient way of structuring a discussion is simply to go through a validated blank directive, using it as a worksheet (19). The sections can be gone through systematically. Using a pencil rather than a pen to fill in the patient's wishes, and having the pencil in the patient's or proxy's hand, can help to emphasize explicitly that in this discussion the directive is being used as a worksheet and not a final document. When scenario-based documents are used, it is possible to start the discussion in something like the following fashion:

> Let's look at these standardized circumstances. You will go through one or two and then perhaps another one or two more. You can then do the rest later.
>
> Imagine this first case in the worksheet. You are in a coma with no awareness. Assume there is a chance that you might wake up, but it isn't likely, and recovery may involve serious disability.
>
> Some people would want us to withdraw treatment and let them die, others would want us to attempt everything possible, and yet others would want us to try to restore quality of life but stop treatment if it was not working. What do you think your goals for medical care would be?

Useful scenarios to have the patient and family go through include (a) a coma with a small chance of recovery (as above), (b) a persistent vegetative state, and (c) a moribund state with waxing and waning consciousness. In each scenario, the patient's goals for care are selected and then illustrated with some selected intervention preferences. The commonly considered intervention preferences are (a) resuscitation, (b) mechanical respiration, (c) chemotherapy or radiation therapy, (d) renal dialysis, (e) major surgery, and (f) artificial nutrition/hydration. In addition, preferences regarding (g) simple diagnostic tests and (h) antibiotics provide useful information. Finally, preferences should be discussed by the patient and family regarding comfort measures. Most people can also say whether pain control or being alert and unconfused to the last possible moment is more important to them. Although not a great deal of time need be spent on informed consent for each intervention, it may be wise to provide brochures on the interventions for patients to review on their own time. Nonetheless, emphasize that deciding on goals for care is more helpful than almost any other specific intervention decision (14).

The first three or so scenarios should be standard scenarios designed to cover the major situations commonly encountered when advance directives pertain. Then two or three additional scenarios can be used that are tailored to the patient. One may be created by the physician, based on the patient's illness and expectable circumstances (29). Another may be created by the patient if he or she wishes, based on what the patient considers to be a state worse than death that has not already been covered in previous scenarios (30). It can also be important to consider a scenario in which the patient is in his or her current health and acquires a new, life-threatening illness involving incompetence.

After these scenarios, patients can be asked what they would consider to be the best to be hoped for from the dying process. Most can say, for instance, that they want enough time to settle things with people they are involved with, that they want to have done one particular thing, or that they want to be in a particular place. Elicitation of these images of a good dying should not be construed as promises to fulfill them. Rather, the physician should tell the patient that the images may help in orchestrating care that frees the patient as much as possible to do as he or she wishes with the last stages of life, before unconsciousness or death occur.

There are certain key positions that patients should be encouraged to articulate during or after their consideration of the scenarios. One is their position on withholding versus withdrawing life-sustaining therapy. Some people have strong positions on the distinction or lack thereof between the two. It is well to have a specific indication whether or not an unwanted intervention, if in place already, should be withdrawn. Another topic that can be included in the scenarios is the place of pain control. Use of pain medications intended to control pain but with a known side effect of hastening death is generally considered morally acceptable. Physician-assisted suicide, while not generally accepted, is receiving wide attention, and it may be helpful to clearly articulate preferences and positions on this matter. Physicians who have patients requesting actions they cannot condone should advise the patients of the fact at this early stage. Similarly, the proxy should raise objections at this stage, if necessary.

Even if the physician is involved in structuring most of the discussion, the entire process need take no more than 15 minutes once the physician has gained experience with it. The intent is not to reach final resolution or to elicit extended narratives. Rather, it is to identify the key issues that patients should think about and to provide them with a good method for recording their preferences. Nonetheless, during these steps patients commonly communicate deeply held values. Witnessing such expressions can give physicians a strong sense of the privilege of caring for patients, and the knowledge that ensues about how health issues fit with the individual patient's sense of meaning in life can be of great practical importance. Reciprocally, patients can feel clearer, more understood, and confident.

Patients should be encouraged to absorb the informational materials and talk over all the issues with their family, friends, pastor, lawyer, counselor, or whomever they consider to be relevant. The patient can then prepare a statement, preferably in a fashion that includes a validated advisory form and a statutory form that can then be stapled together if they are not already combined.

Recording the Document

Once the patient has completed the essential personal discussions outside the physician's office, he or she can bring the document in for final review by the physician. At this point, the physician can check for medical misconceptions and major changes that may need inquiry. This should take only a few moments in most cases. It is useful to have a space where the physician can cosign the document (31). This signature should not be a requirement, but its presence fosters the physician's involvement and carries an important implicit message of partnership between patient and physician.

Updating the Document

Documents should be reviewed at routine intervals. For a patient who has undergone a cure or for whom the prognosis is good, this review should occur every 1 to 5 years and after major life changes such as childbirth, marriage, divorce, significant health status changes, bereavement, and important experiences of others' ill health. Most reviews will be rapid. Specific treatment decisions are about as durable as other major life decisions such as marriage (32,33,34 and 35). When a patient shows a particularly high level of instability, this may indicate incompetence for advance decision-making, and the physician should review the matter, perhaps advising simple designation of a proxy instead of instructional directives.

Applying the Document to Real Decisions

Certain patterns of decisions have high degrees of predictability. If a patient's prior directives do not cover the decision at hand, it may well be possible to extrapolate from the preferences that are provided in the directive. Such predictions can be far more accurate than unguided judgments. Decline of less invasive interventions predicts decline of more invasive interventions, and acceptance of more invasive interventions predicts acceptance of less invasive interventions. Acceptance of intervention in poor-prognosis scenarios predicts acceptance in better-prognosis scenarios, and decline in better-prognosis scenarios predicts decline in poorer prognoses. The use of simple calculations can even provide probability estimates of specific decisions, which, when very high or very low, can be a comforting guide to proxy decision-makers (36). This approach is illustrated and necessary reference statistics are provided in Appendix 63-2 and Table 63-2-1 and Table 63-2-2.

Pitfalls and Preventive Measures

A common pitfall is to omit advance care planning discussions altogether. Another variation on this theme is to mistakenly suppose that a “DNR discussion” is sufficient advance care planning. Discussing cardiopulmonary resuscitation and use of a DNR order in the absence of considering a range of scenarios and goals for care is often needlessly frightening for patients, considering as it does only the moment of death, and often yields unstable decisions and poor guidance to providers. If a clinician cares for a patient for whom a DNR order is written without comprehensive orders, such as are outlined in a Physician's Orders for Life Sustaining Treatment form, this should prompt a review of advance care planning with that patient.

As advance directives gradually come into more general use, common pitfalls are emerging (37). Assessment of a patient's competence to undertake advance care planning can be difficult if profound psychological issues or psychiatric diagnoses are involved. Occasionally, for instance, a patient will show major inconsistency in treatment plans or will ask for extremes of no treatment or undue intervention. These may be indications of ineffective emotional adjustment to medical circumstance. Although perhaps not strictly incompetent for completing advance directives, these patients may do better using proxy designation rather. than instructional directives to

preserve flexible decision making. As an alternative, advance care planning can be deferred or updated frequently until psychotherapy or other assistance has secured better emotional adjustment.

A further problem is noninclusion of relevant parties at early stages of planning. Noninclusion of the proxy or of family members or close friends who have divergent opinions can lead to fractured decision making. Noninclusion of the physician can lead to inadequate sensitization of the physician to the patient's thinking. For instance, a recent major study showed that when a nurse is the main communicator in advance planning, the physician's understanding of the patient's wishes is not improved (38).

Poor informed consent and documentation constitute another pair of pitfalls. For example, a patient may express a strong desire to avoid perpetual dependence on a respirator, but the wording of the advance directive may indicate that a respirator should never be used. In the event of reversible pneumonia, the patient may well want temporary use of a respirator. A properly validated directive should require this kind of distinction, and physicians should ensure this minimum level of patients' understanding. Physicians should check the document for improbable statements and ask patients to briefly state their wishes in free words, checking for correspondence with medical possibilities.

Perhaps the most common pitfall of all is activation of advance directives before patients have reached a wishless state and sometimes even before they have reached an incompetent state for the decision(s) at hand. A widespread tendency to avoid direct communication with patients appears to exacerbate this problem. Advance directives, as distinct from their predecessor, the DNR order, usually have no authority when they are first written and must not be activated until the patient is decisionally incapacitated and wishless.

A final, crucial pitfall is poor application of wishes to eventual decisions. Some studies have indicated that physicians rather commonly override advance directives (39). Whether this is because patients are decisionally incapacitated but not wishless, or because proxy opinions persuade physicians more than the patient's advance directives, or for other reasons, is not well studied. Nonetheless, if a patient has a validated advance directive that uses scenarios and specific intervention choices, extrapolation to unstated decisions can be accomplished with considerable accuracy in many cases.

BROADER USES

Structured Deliberation

An unforeseen benefit brought about by the idea of advance directives was a general increase in attention to the questions of how patients' health care values can be elicited, understood, documented, and used as the driving force behind therapeutic decision making. In a sense, the field emerged from a desire to move the medical question from, “What is the right decision?” to, “Who should make the decision?” with the intended answer being “the patient.” However, as the desirability of multilateral decision making became more accepted, the question has become, “What is the right kind of deliberative process for the decision?” This latter question is potentially relevant to a wide range of decisions and circumstances. In delineating a set of validated worksheets and structured deliberations for advance directives, the concept of structured deliberation for a wide range of medical decisions and approaches has emerged (40,41).

Structuring Other Care Plans

The use of care plans need not be limited to scenarios involving incompetence and wishlessness. Plans can usefully be made for situations involving no loss of competence as well. Nursing home and hospice facilities often make use of such plans. A common example is prior decision-making regarding transfer to a hospital facility in case of medical deterioration. Those who decline may have a written “do not hospitalize” order. Similar decisions about levels of medical care within the facility can also be made. For instance, some patients may elect comfort care only, whereas others may elect simple diagnostic maneuvers but no invasive ones, and others may elect full aggressive care. Corresponding orders and/or notes can be written in patients' records. Such decisions must always be subject to change if the patient wishes, just as advance directives are adjustable while the patient is competent. Nonetheless, such planning provides important communication and often streamlines decision making in the event of otherwise difficult decisions.

Intervention for Turbulent Thought Processes

Patients in difficult medical circumstances often face existential decisions. Turbulent emotions and turbulent thinking are common. For instance, a patient may understand that he or she has incurable cancer and, therefore, decline chemotherapy, but, when faced with the need to make a decision about resuscitation, may be precipitated into an emotional crisis by the sense of imminent death or impending abandonment and may decline a “DNR” order. Such decisions are often perplexing to providers, and discord between parties readily ensues. Discord over goals or treatment decisions should alert physicians to the likelihood that patients are facing emotional and moral turbulence. A structured dialogue can be very helpful. The preset scenarios in a validated, generic, advance directive provide an excellent structure. By going back over preset scenarios that the patient knows were designed independently and that cover questions likely to be relevant (because the document is validated), the physician may be able to discern the structure of the patient's nonturbulent moral thought. With the more stable structure returned, it is possible to reapproach a scenario that is tailored to the patient and, finally, the patient's current situation. Often, the patient no longer feels threatened by the sense of imminent mortality, and coherent thought processes and decisions can occur again. If these discussions are conducted in the presence of the proxy and other relevant care providers, there can be a refocusing of the entire group of providers on the retrieved coherent plan. Difficult personal interactions and time-consuming confusions can be put aside, allowing people to get on with the business of preparing for departure on a personally meaningful level.

Structured deliberations such as these can also provide an approach to patients who request euthanasia or physicianassisted suicide. Some patients may have firm and persuasive reasons for requesting such actions, but many patients are, in fact, seeking something else. Some seek control, some attempt to avoid pain, and some try to address concerns about being a burden or being abandoned. A structured path through scenarios allows patients to assert control and gain assurances that pain can be controlled in the great majority of cases, that there are ways of planning for burden and nonabandonment, and that there are ways to exit this world without active euthanasia or assisted suicide. Some physicians find active euthanasia morally defensible in some instances, and others do not. But all must agree that patients who request it erroneously, who are actually seeking care, should be identified and guided toward the actions they really desire. Structured deliberations can provide a sensitive, professional, and efficient method to help patients understand their own desires. They also provide the physician with a chance to communicate explicitly what their moral position is; physicians who do not find active euthanasia or physician-assisted suicide acceptable can make this clear in the supportive setting while simultaneously making clear what comfort care they can offer.

Limitations and Future Directions

As important as advance directives may be, they have clear limitations and should not be construed as a panacea for decision-making about life-sustaining interventions. Especially in the case of moderately demented patients or otherwise decisionally incapacitated but not wishless patients, advance directives offer no more than tangible evidence of one among other perspectives to be weighed in the decision. Even for wishless patients, advance directives provide a way to augment the honoring of surviving interests, but they do not offer perfect evidence of all relevant wishes.

No Evidence for Cost Savings

Some advocates have suggested that the use of advance directives can effect considerable cost savings. This perspective has been motivated by the assumption that their use would help avoid unwanted and costly interventions and, therefore, help reduce the costs of medical care. While end-of-life care is very costly, there is evidence that patients tend to opt for more treatment than physicians and nurses, and that proxies opt for even more intervention (42,43). In addition, although hospice and palliative care have traditionally been less costly than hospital care for dying patients, these populations are self-selecting. A randomized, controlled trial found no cost savings, perhaps indicating that patients, taken in the aggregate, may be getting more or less the degree of intervention that they want (44,45). Individual matches with patients' wishes are, however, found to be poor in many studies, and advance planning should continue with the goal of closing this gap. These motivations for advance planning have overwhelming, independent merit and should not be confused with false economic incentives.

When Patients Have No Advance Directive

About half of all patients have an estate will. If even this form of well-accepted planning for death is not used by more patients, it is likely that advance directives will also have a similar “ceiling.” To meet the objective of attempting to match decisions with patients' prior preferences, it can be helpful to have supplementary approaches (46). In circumstances when the patient comes from a population of patients whose preferences have been studied and documented, it is possible to refer to those data to help guide decisions for them. Thus, if it is known that the patients registered at the hospital in question declined resuscitation for the situation at hand in 85% of instances, the proxy may find this useful guiding information. In cases when the proxy has no idea how to speak on behalf of the patient, the physician may indicate that the greatest likelihood of matching the patient's prior wishes, if only the patient had had a chance to articulate them, will be by following the majority preferences of others. Naturally, these default guidelines should not be coercive or replace valid personal directives.

APPENDIX 63-1

THE MEDICAL DIRECTIVE

INTRODUCTION

As a part of a person's right to self-determination, every adult may accept or refuse any recommended medical treatment. This is relatively easy when people are well and can speak. Unfortunately, during serious illness they are often unconscious or otherwise unable to communicate their wishes—at the very time when many critical decisions need to be made.

The Medical Directive allows you to record your wishes regarding various types of medical treatments in several representative situations so that your desires can be respected. It also lets you appoint a proxy, someone to make medical decisions in your place if you should become unable to make them on your own.

The Medical Directive comes into effect only if you become incompetent (unable to make decisions and too sick to have wishes). You can change it at any time until then. As long as you are competent, you should discuss your care directly with your physician.

COMPLETING THE FORM

You should, if possible, complete the form in the context of a discussion with your physician. Ideally, this should occur in the presence of your proxy. This lets your physician and your proxy know how to think about these decisions, and it provides you and your physician with the opportunity to give or clarify relevant personal or medical information. You may also wish to discuss the issues with your family, friends, or religious mentor.

The Medical Directive contains six illness situations that include incompetence. For each one, you consider possible interventions and goals of medical care. Situation A is permanent coma, B is near death, C is with weeks to live in and out of consciousness, D is extreme dementia, E is a situation you describe, and F is temporary inability to make decisions.

For each scenario, you identify your general goals for care and specific intervention choices. The interventions are divided into six groups: (a) cardiopulmonary resuscitation or major surgery; (b) mechanical breathing or dialysis; (c) blood transfusions or blood products; (d) artificial nutrition and hydration; (e) simple diagnostic tests or antibiotics; and (f) pain medications, even if they dull consciousness and indirectly shorten life. Most of these treatments are described briefly. If you have further questions, consult your physician.

Your wishes for treatment options (I want this treatment; I want this treatment tried, but stopped if there is no clear improvement; I am undecided; I do not want this treatment) should be indicated. If you choose a trial of treatment, you should understand that this indicates you want the treatment *withdrawn* if your physician and proxy believe that it has become futile.

The Personal Statement section allows you to explain your choices, and say anything you wish to those who may make decisions for you concerning the limits of your life and the goals of intervention. For example, in situation B, if you wish to define “uncertain chance” with numerical probability, you may do so here.

Next, you may express your preferences concerning organ donation. Do you wish to donate your body or some or all of your organs after your death? If so, for what purpose(s) and to which physician or institution? If not, this should also be indicated in the appropriate box.

In the final section, you may designate one or more proxies who would be asked to make choices under circumstances in which your wishes are unclear. You can indicate whether or not the decisions of the proxy should override your wishes if there are differences. And, should you name more than one proxy, you can state who is to have the final say if there is disagreement. Your proxy must understand that this role usually involves making judgments that you would have made for yourself, had you been able, and making them by the criteria you have outlined. Proxy decisions should ideally be made in discussion with your family, friends, and physician.

WHAT TO DO WITH THE FORM

Once you have completed the form, you and two adult witnesses (other than your proxy) who have no interest in your estate need to sign and date it.

Many states have legislation covering documents of this sort. To determine the laws in your state, you should call the state attorney general's office or consult a lawyer. If your state has a statutory document, you may wish to use the Medical Directive and append it to this form.

You should give a copy of the completed document to your physician. His or her signature is desirable but not mandatory. The directive should be placed in your medical records and flagged so that anyone who might be involved in your care can be aware of its presence. Your proxy, a family member, and/or a friend should also have a copy. In addition, you may want to carry a wallet card noting that you have such a document and where it can be found.

MY MEDICAL DIRECTIVE

This Medical Directive shall stand as a guide to my wishes regarding medical treatments in the event that illness should make me unable to communicate them directly. I make this Directive, being 18 years or more of age, of sound mind, and appreciating the consequences of my decisions.

SITUATION A

If I am in a coma or a persistent vegetative state and, in the opinion of my physician and two consultants, have no known hope of regaining awareness and higher mental functions no matter what is done, then my goals and specific wishes—if medically reasonable—for this and any additional illness would be:

☐ prolong life; treat everything
☐ attempt to cure, but reevaluate often
☐ limit to less invasive and less burdensome interventions
☐ provide comfort care only
☐ other (please specify): _____

(Please check appropriate boxes)

	I want	I want treatment tried. If no clear improvement, stop.	I am undecided	I do not want
1. **Cardiopulmonary resuscitation** (chest compressions, drugs, electric shocks, and artificial breathing aimed at reviving a person who is on the point of dying). _____		Not applicable		
2. **Major surgery** (for example, removing the gallbladder or part of the colon). _____		Not applicable		
3. **Mechanical breathing** (respiration by machine, through a tube in the throat). _____				
4. **Dialysis** (cleaning the blood by machine or by fluid passed through the belly). _____				
5. **Blood transfusions or blood products.** _____		Not applicable		
6. **Artificial nutrition and hydration** (given through a tube in a vein or in the stomach). _____				
7. **Simple diagnostic tests** (for example, blood tests or x-rays). _____		Not applicable		
8. **Antibiotics** (drugs used to fight infection). _____		Not applicable		
9. **Pain medications, even if they dull consciousness and indirectly shorten my life.** _____		Not applicable		

SITUATION B

If I am near death and in a coma and, in the opinion of my physician and two consultants, have a small but uncertain chance of regaining higher mental functions, a somewhat greater chance of surviving with permanent mental and physical disability, and a much greater chance of not recovering at all, then my goals and specific wishes—if medically reasonable—for this and any additional illness would be:

☐ prolong life; treat everything
☐ attempt to cure, but reevaluate often
☐ limit to less invasive and less burdensome interventions
☐ provide comfort care only
☐ other (please specify): _____

(Please check appropriate boxes)

	I want	I want treatment tried. If no clear improvement, stop.	I am undecided	I do not want
1. **Cardiopulmonary resuscitation** (chest compressions, drugs, electric shocks, and artificial breathing aimed at reviving a person who is on the point of dying). _____		Not applicable		
2. **Major surgery** (for example, removing the gallbladder or part of the colon). _____		Not applicable		
3. **Mechanical breathing** (respiration by machine, through a tube in the throat). _____				
4. **Dialysis** (cleaning the blood by machine or by fluid passed through the belly). _____				
5. **Blood transfusions or blood products.** _____		Not applicable		
6. **Artificial nutrition and hydration** (given through a tube in a vein or in the stomach). _____				
7. **Simple diagnostic tests** (for example, blood tests or x-rays). _____		Not applicable		
8. **Antibiotics** (drugs used to fight infection). _____		Not applicable		
9. **Pain medications, even if they dull consciousness and indirectly shorten my life.** _____		Not applicable		

APPENDIX 63-2

EXTRAPOLATING STATED PREFERENCES

It is often necessary to infer a prior preference, since advance directives cannot foresee all possible decisions. In addition to using the general rules noted in the text of the chapter, it may be possible to use what a patient did state along with population preference data to calculate the probability that a particular prior preference would have been made if the patient had considered it. For many physicians and proxies, these calculations are reassuring.

Survey preference data from patients completing the Medical Directive provide prior odds for treatment preferences (Table 63-2-1). The same data allow particular preferences to be used as a “test” for other particular preferences. Each decision pair has a likelihood ratio that has been calculated from this data set. So, if the patient stated a prior preference that fits the test preference, the likelihood for all other decisions on the Medical Directive can be found (Table 63-2-2 and its accompanying explanatory footnotes). Together, the prior odds of a preference and the likelihood ratio of the relevant preference pair can be used to calculated the posterior odds that a patient would have had a particular preference (36).

Take the following example:

A patient who is unconscious and has a small chance of recovery has an advance directive stating that (s)he does not want artificial feeding in such a situation, but the question is whether to write a “Do Not Resuscitate” order. The family have no idea what the patient would have wanted. From Table 63-2-1 we see that the prior odds of declining resuscitation in this circumstance is 1.2 (55% of the population declined it). We also know from Table 63-2-2 that the likelihood ratio for this decision is 12.6. Therefore, the posterior odds are 1.2 × 12.6 = 15.1 that (s)he would have declined resuscitation. Therefore, the posterior probability that (s)he would have stated a wish to decline cardiopulmonary resuscitation in an advance directive is 15.1/(1 – 15.1) = 94%.

	Coma/chance		PVS		Dementia		Dementia/terminal	
Rx	Decline	Accept	Decline	Accept	Decline	Accept	Decline	Accept
abx	0.9	1.1	3.1	0.3	1.9	0.5	3.3	0.3
blood	1.3	0.9	4.2	0.3	2.5	0.4	4.8	0.2
cpr	1.3	0.8	4.8	0.2	2.4	0.4	4.7	0.2
dnr	0.8	1.2	3.7	0.3	2.4	0.4	4.2	0.2
dx	0.9	1.1	2.3	0.4	1.6	0.6	2.7	0.4
feed	1.2	0.8	4.8	0.2	2.7	0.4	4.2	0.2
iv	1.1	0.9	3.3	0.3	2.4	0.4	4.6	0.3
ommaj	1.6	0.6	5.1	0.2	3.0	0.3	5.3	0.2
ommin	1.2	0.8	4.1	0.2	2.2	0.5	3.9	0.3
dialysis	1.3	0.8	4.1	0.3	2.6	0.4	4.4	0.3
resp	1.2	0.8	4.0	0.3	2.7	0.4	4.8	0.2

abx, antibiotics; blood, blood transfusions; coma/chance, coma with a chance of recovery; cpr, cardiopulmonary resuscitation; dementia/terminal, dementia with terminal illness; dialysis, peritoneal or hemodialysis; dnr, invasive diagnostics; dx, noninvasive diagnostics; feed, artificial tube feeding; iv, intravenous fluids; ommaj, major operations; ommin, minor operations; PVS, persistent vegetative state; resp, mechanical respiration.
The prior odds for preferences are derived from population data that have been published elsewhere (47). The assumption is that prior odds of a given choice = (proportion of population with that choice)/(1 − proportion of population with that choice).
Some proxies or physicians will have reason to understand that the patient was not well represented by the population data. In these cases, if a calculation is still desired, a numerical estimate of the prior odds will have to be derived from whatever information is available.

TABLE 63-2-1. PRIOR ODDS FOR TREATMENT CHOICES

TABLE 63-2-2. DEFINING AND USING LIKELIHOOD RATIOS FOR PREFERENCE PAIRS

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WITHHOLDING AND WITHDRAWING TREATMENT: THE DOCTOR-PATIENT RELATIONSHIP AND THE CHANGING GOALS OF CARE

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Medical technology and sophisticated therapeutics have enabled physicians to prolong life—or, at the very least, to postpone death—in the face of serious illness. Patients thought to have terminal conditions less than a century ago are now living longer in our intensive care units (ICUs) and hospitals. This increased survival may not always translate into improved quality of life. Our technological capabilities have allowed us to adopt an aggressive approach to "curing" disease and maintaining life at all costs. And when our best efforts fail, we are ill-prepared as a society to deal with the lasting social and emotional consequences. It has become increasingly difficult for patients, families, and health care workers to decide when to stop "saving" a life and when to start the difficult process of preparing for death. What defines a "dying" patient? Must a patient actively decide to forego curative therapy to receive excellent palliative care? More and more often, these decisions are being made in hospital settings: 60% of deaths in the United States are in hospitals (1), and of these, up to 75% occur in the setting of decisions to withdraw or withhold life-sustaining therapies (2). The moment and timing of death is now managed, controlled, and negotiated, often by physicians who have had little formal training in the complexities of decision making or the clinical demands of end-of-life care.

This chapter begins by situating current debates about end-of-life care against the background of the dramatic social changes of the last decade. We then provide a review of the foundational ethical and legal framework governing decisions to withhold and withdraw life-sustaining therapies in the United States. The importance of the doctor-patient relationship in understanding (and enhancing) shared decision making on the trajectory to death is high-lighted. Increasing cultural diversity—a feature of much of the United States and many First World countries— provides a challenge to our fundamental assumptions about end-of-life decision making. Has the bioethics community been too insistent that patients make decisions requiring that they embrace death to receive first-rate palliative services? Finally, barriers to effective communication and approaches to improving end-of-life decision making are discussed. Although we have achieved significant progress as a result of increased attention to end-of-life care, the goal of translating the legal and ethical ideals described here remains incomplete.

SOCIAL AND HISTORICAL CONTEXT

Studying and commenting on death and dying has become a growth industry in the United States. But as little as 20 years ago, the words were rarely spoken outside of the medical "fringe"—for example, in the hospice movement, which developed outside mainstream medical practice and remained there until it successfully lobbied for the Medicare hospice benefit. In marked contrast, death is now defined as a major medical *problem* in need of a solution. And the problem has moved from the periphery of health care, a concern often delegated to nursing or social work, to a position closer to the center of medical practice. Evidence of this transformation—still incomplete—abounds. The Institute of Medicine (of the National Academy of Sciences) issued a major report on methods to improve care for the dying in 1997 (3), and a second report on the death of children appeared in 2002. The American Board of Internal Medicine has published an extensive series of recommendations and suggestions about best practice in the *Annals of Internal Medicine* (4). The American Medical Association conducted a nationwide education campaign to reach as many practicing physicians as possible in an effort to improve their practice in this area, and a similar effort exists within the nursing profession. Hospice and Palliative Medicine has become a recognized specialty in the United States. Major philanthropies have supported this work. The Robert Wood Johnson Foundation has established a national public relations campaign, titled "Last Acts," which aims to transform the culture of dying in the United States. George Soros' Open Society Institute created the "Project on Death in America," including a program to promote faculty scholars in U.S. schools of medicine (coauthors Crawley and Koenig have both received these awards). Perhaps of most symbolic significance, the National Institutes of Health have, for the first time, funded research initiatives in palliative care, primarily in symptom management, albeit on a small scale compared to its overall budget.

The primary solution to the problem of death and end-of-life care over the past three decades has been to institute bioethics practices that shift decisional authority from health care providers to patients. Patients must make concrete "decisions" about resuscitation, the transition from curative therapies to comfort care, and life-extending technologies such as ventilators and tube feeding. A key element in the tool kit of interventions is end-of-life planning, generally in the form of legal instruments like the durable power of attorney for health care. Perhaps not surprisingly, a $32 million, multisite, multiyear study—with the acronym SUPPORT—called into question the foundational bioethics paradigm (5). An intervention that included "state-of-the-art" procedures to elicit patients' preferences for care and to inform physicians of patient choices was deemed a failure. In spite of the results of the SUPPORT study, most of the national programs described continue to incorporate a fairly standard model of end-of-life decision making emphasizing patient choice. There is enormous reluctance to move away from the normative models developed over the past 30 years.

Our current practices are the result of careful ethical reflection by scholars in medicine, law, philosophy, and social science (6,7). These deliberations took place in dialogue with an important series of court decisions reviewed in the section Ethical Principles and Legal Standards. The result was a set of bioethics practices that now exerts enormous influence on clinical decisions at the end of life. The attention paid here to these seminal legal rulings should not lead to the conclusion that court intervention is necessary or desirable when difficult end-of-life choices emerge. Rather, in most instances decision making is best handled within the immediate clinical setting. Most bioethics scholars agree that courts should only be called on in the face of irresolvable conflict, and that even then a clear-cut resolution may not be forthcoming.

ETHICAL PRINCIPLES AND LEGAL STANDARDS

We argue that in the United States the interdisciplinary field of bioethics has come to dominate clinical practice about decision making in end-of-life care. Indeed, the issues associated with care of the dying have been central to the growth of bioethics, propelling its establishment as a field (8). Preserving patient autonomy has been the primary principle guiding many innovations, such as the use of advance directives to aid decision making for incompetent patients. Other foundational principles—beneficence, nonmaleficence, and justice—also influence decisions about withdrawing and withholding treatments in the United States (9,10). However, autonomy, or the right to selfdetermination, generally serves today as the cornerstone of ethical decisions in medicine. The principle of individual autonomy expresses the right of the competent individual to control decisions about his or her body. Although this includes the right to refuse life-sustaining therapies, it does not necessarily imply a complementary right to demand medically unnecessary, ineffective, or harmful therapy.

In the past quarter century, Western bioethics has emphasized the importance of the individual and individual choice (6). Qualities assumed to be present in the autonomous person include an ability to understand medical information, an awareness of individual preferences and values, and the capacity to communicate these values effectively. To facilitate the decision-making process by such competent individuals, physicians have a moral and ethical obligation to inform patients of their diagnosis and prognosis and to discuss available therapeutic options, including potential risks and benefits. Thus full disclosure of information or "truth-telling" by physicians is central to the principles of informed consent and informed refusal that have formed the basis for court rulings on withdrawal and withholding of medical treatment (11,12). It is clear from this brief description that informed decision making can be fraught with difficulties, chief among which is the lack of understanding and effective communication among physicians, patients, and their families. Speaking openly about death is challenging for all parties. We highlight some of these barriers to ideal communication later in this chapter.

In the United States, the legal justification for withholding and withdrawing treatments is based on the doctrines of informed consent and informed refusal (11,12). These principles state that except in emergency situations, all treatments should be initiated with the agreement of patients or their surrogate decision-makers, and that patients or surrogates have the right to refuse any or all treatments, even life-sustaining treatments. These fundamental rights are embodied in common law and legal statutes, and reflect basic protections provided by the United States Constitution (13).

The right to refuse medical treatment has so dominated recent discourse on end-of-life decision making that it is hard to remember that not long ago it was considered unethical and illegal for physicians and patients to terminate life-supporting therapies (14). The right of competent patients to refuse therapy was established in the 1984 case of *Bartling v. Superior Court* (15), in which the California Court of Appeals affirmed that mechanical ventilation could be discontinued at the request of the patient, despite objections by the physicians involved and the hospital providing care. Similarly, in *Bouvia v. Superior Court* (16), the California Court of Appeals established that a competent patient could refuse hydration and nutrition. Although the common law and statutory bases vary from state to state, a competent patient's right to refuse life-sustaining treatment is currently recognized by all American courts (12).

The ethical and legal considerations discussed have focused on the competent adult patient; but what if the adult patient lacks decision-making capacity? Assessment of decision-making capacity, sometimes called *competence*, is particularly complex when issues of withholding or withdrawing therapy are under review, because of the import and potential consequences of the decisions. (See Chapter 62, Assessment of Decision-Making Capacity.) In general, patients are not considered either globally competent or incompetent to make decisions; rather, the evaluation of capacity must be specific to the choice at issue. A patient who is unable to manage his or her financial affairs may be able to make informed choices about her personal care or other key components of palliative medicine. Patients who lack decision-making capacity continue to have the right to forego or limit therapy, if they have expressed this preference beforehand. However, a surrogate decision maker, rather than the patient, must exercise this right. In the ideal situation, a patient can exert control over these decisions by completing an advance directive, generally including the identification of a surrogate decision maker during periods of relative good health and clear thinking. In the absence of such a written directive or of an available and informed proxy decision maker, two standards are used to aid the decision-making process: the principles of “substituted judgment” and “best interest” (17).

The substituted judgment standard holds that decision makers, often family members or close friends, are not making choices based on their own values and beliefs; rather, their role is to “substitute” for the patient by expressing the patient's previously stated wishes. Because of widespread cultural reluctance to engage in active planning for one's death, friends or family members designated as legal surrogates often do not have clear-cut ideas of a patient's wishes. This occurs for many reasons. Frequently no discussion has taken place, especially if surrogates have been delegated through routine legal or estate planning, rather than in conversation with a health care provider. But even a surrogate who has a general understanding of the patient's values may find it difficult to translate stated preferences into clear-cut decisions once the patient is no longer able to decide for him- or herself. If the decisions of the surrogate are not in accord with previously stated patient wishes, or if there is disagreement among family members as to the best course of action, every effort should be made to reach a consensus. If a patient's wishes were not clearly stated or are unknown, then surrogate decision makers should rely on their knowledge of patient values and goals to determine what the patient would desire under existing circumstances. Finally, if the substitute decision maker is unable to make such choices based on the patient's prior statements or values, the “best interest” standard can be used to guide decisions. The surrogate decision maker, in collaboration with physicians and other health care workers, should balance the benefits of initiating or continuing a life-sustaining therapy with its perceived burdens to the patient. If the benefits outweigh the burdens, then the therapy should be continued; otherwise it should be discontinued (17,18). When incompetent patients do not have advance directives or substitute decision makers, the health care team (and rarely, the addition of a designated ombudsperson or courtappointed decision maker) should use the “best interest” standard to make treatment decisions. These principles echo the U.S. courts' rulings in various cases. Although theoretically forceful and legally sound in the clinic, these prescriptions and bioethics practices may be difficult to follow.

The legal principles of informed consent and informed refusal were applied for the first time to the care of incompetent patients during the 1970s in the *Quinlan* case (19). Here the New Jersey Supreme Court ruled that the patient, who was in a vegetative state, had the right to refuse continuation of mechanical ventilation. Because she could not exercise this right directly, her parents could act as surrogate decision makers and make a “substituted judgment” to guide her care. Similarly, in *Barber v. Superior Court* (20), the California Court of Appeals determined that two physicians charged with murder had not committed a crime when, with the permission of the patient's spouse and children, they discontinued artificial nutrition and hydration sustaining the life of the comatose patient. In its decision, the Court not only reinforced the substituted judgment principle set forth in *Quinlan* but also emphasized that all medical interventions should be evaluated according to benefits and burdens to patients. Based on the “best interests of patients,” if the burdens outweigh the benefits, then a particular treatment should be withheld or withdrawn.

Although the rights of incompetent patients to refuse life-sustaining treatments are now uniformly acknowledged in this country, the states vary in their regulations for selecting surrogates and determining what decisions surrogates can make. Some states have statutes that establish a hierarchy of decision makers among family members and relatives. For example, these guidelines specify who a clinician should turn to for assistance with decision making for an incompetent patient, specifying whether to give priority to a grown child or a spouse. There is general agreement that decisions should be based on patients' wishes and values; however, some states require a “high degree of certainty” before allowing surrogate decision-makers to withdraw or withhold treatment (12). The State of Missouri, for example, requires “clear and convincing evidence” of an incompetent patient's wishes before such end-of-life decisions. This position was established in the *Cruzan* case (21), in which the parents of a young woman diagnosed as persistently vegetative requested removal of the feeding tube from their daughter. The Missouri Supreme Court denied this request based on the facts of the case and the State's interest in the preservation of life. The U.S. Supreme Court, in its first consideration of the issue of withholding and withdrawing life-sustaining treatments, affirmed the decision of the Missouri Supreme Court, and by supporting the standard of requiring “clear and convincing evidence” of patient's wishes allowed states to restrict the role of surrogate decision makers. In effect, the Supreme Court allowed each state to decide how strong the evidence of patient wishes needs to be before proceeding with the decision to withdraw life support.

The *Cruzan* case is particularly important for its recognition of the principles of informed consent and informed refusal. In an opinion delivered by Chief Justice Rehnquist, the Supreme Court acknowledged prior rulings establishing the right of a competent person to refuse medical treatment under the Fourteenth Amendment to the Constitution: “The Fourteenth Amendment provides that no State shall 'deprive any person of life, liberty, or property, without due process of law.' The principle that a competent person has a constitutionally protected liberty interest in refusing unwanted medical treatment may be inferred from our prior decisions” (21).

The *Cruzan* ruling acknowledged decisions put forth by prior cases (19,20,22) and declared that the legal principles stated apply to all medical interventions, without distinguishing between “ordinary” and “extraordinary” treatments. Thus, in the eyes of the court, withdrawing and withholding of mechanical ventilation is no different from decisions to withdraw dialysis or nutrition and hydration.

One point discussed in the *Cruzan* case is worthy of mention: The general consensus among bioethicists and the U.S. legal system is that there is no legal and ethical distinction between withholding and withdrawing of lifesustaining therapies (17,22,23). Despite this agreement, health care workers and families have traditionally found it more difficult emotionally to withdraw life support rather than to withhold treatment. Religious and cultural views certainly influence this distinction. An awareness of these views is important in any end-of-life discussions with patients and their families.

Problems in Applying the Model

Although the ethical and legal principles discussed thus far appear clear-cut, making decisions for patients in practice, especially patients lacking clear decision-making capacity, is a difficult task. More and more, our technologies enable us to delay death in patients with advanced diseases. Many treatments offer only marginal benefit, and with a rapidly aging patient population suffering from multiple chronic and disabling illnesses, predicting which exacerbation will bring on a patient's final episode of ill health is possible only in retrospect. When these exacerbations occur, many patients lose the ability to make informed decisions about their own health care, or perhaps clear-cut preferences simply have never been voiced. The important responsibility of guiding treatment decisions falls on the shoulders of substitute decision makers. Surrogate decision makers do not make their decisions in a vacuum. Ideally, the patient's wishes and values should govern the decision-making process; however, the moral and religious convictions of the decision maker, family dynamics and cultural influences, and (rarely) possibilities of secondary gain undoubtedly play a role in these decisions. As stated in the *Cruzan* ruling, “There is no automatic assurance that the view of close family members will necessarily be the same as the patient's would have been had she been confronted with the prospect of her situation while competent” (21). A lack of clear and open communication between patients and their families and physicians is in part responsible for the difficulty faced by surrogate decision makers.

Many American families shy away from discussing death and the dying process openly (24). As a result, even patients who feel strongly about limiting life-sustaining therapies may fail to communicate these wishes to loved ones. The minority of adults who express their wishes through advanced directives do so in vague terms, often failing to provide clear guidelines for decisions regarding withdrawal or withholding of specific therapies such as nutrition, hydration, and mechanical ventilation. More important, patients do not discuss these directives with family members or their physicians, thus losing an opportunity to verbally express their values and beliefs and perhaps clarify some ambiguities. In a series of studies reported in 1997, Teno et al. noted that only 12% of patients with advance directives had talked to their physicians before completion of the document (25). Not surprisingly, only 5% of advance directives contained specific instructions about life-sustaining therapies (26). It is very difficult for anyone to select options from a list of imagined life-extending therapies, such as dialysis or intubation; patients often cannot express clear preferences about care in the abstract. In fact, the idea that all patients have clearly expressed preferences for specific interventions is conceptually flawed. More often, preferences emerge as patients interact with their care providers (27).

Given these uncertainties, surrogate decision makers are left with the difficult task of interpreting a patient's previous comments or using their understanding of the patient's goals to make decisions about a situation not previously experienced or considered by the patient. Empirical research using anthropological methods has shown that patients and families often have quite varied understanding of the nature of critical “decisions,” particularly in the ICU setting (28). Because events unfold under extreme time pressure, the medical profession and family members often find themselves at odds over decisions to withdraw and withhold therapies. One of the more challenging conflicts arises when surrogate decision-makers or patients themselves demand therapies that seem useless, unreasonable, or “futile” to the medical team. These conflicts are due in part to differences in treatment goals and values among patients, their decision-makers, the health care team, and the medical institution. Poor communication, uncertainties surrounding disease severity, and high expectations for the success of medical therapy serve to fuel frustrations and

create an environment of mistrust.

Based on the ethical principles of beneficence and nonmaleficence (providing benefit; avoiding harm) and distributive justice (using scarce health care resources fairly), a physician has no ethical obligation to provide treatments that he or she deems medically futile (29). The purpose of life-sustaining interventions is to benefit patients and promote their well-being. Theoretically, futile interventions are those that do not confer any benefit and thus have no intrinsic value. At an operational level, a straightforward definition of futile treatment has proven difficult to implement, because no objective measures of futility exist, and its application in particular cases is inevitably subjective and open to abuse. Arguments in favor of limiting or withholding futile treatments, even against the wishes of patients and families, are also made based on the principle of nonmaleficence. According to this reasoning, health care professionals have a moral obligation to protect the patient from harm; interventions considered futile may cause unnecessary pain and suffering and may have harmful side effects, thus justifying a decision to withhold certain interventions defined as futile, such as resuscitation attempts in seriously compromised patients. Furthermore, health care institutions sometimes limit life-sustaining therapies by establishing policies that restrict access to intensive care or coronary care units, a decision supported by the ethical principle of “distributive justice,” in which use of costly therapies unlikely to provide benefit is not justified from a societal perspective. It is important to remember that decisions about the just allocation of scarce health care resources are best made at the institutional or societal level, and not by any one physician or other health care provider faced with the care of a particular terminally ill patient. Even though this view is widely espoused, health care professionals still experience the troubling dilemma of providing care they deem futile. And some bioethicists have argued that clinicians do have an obligation to consider the “costworthiness” of the interventions they recommend (7).

As discussed, there is no clear definition of medically futile therapy. A narrow definition of medical futility focuses on the “physiological futility” of an intervention. Therapies that do not achieve their physiological goal are futile; withholding these therapies does not cause any harm and may benefit the patient by avoiding painful interventions. The physician's professional training and experience determine whether interventions are physiologically effective. In the ICU, for example, the continued use of vasoactive medication to treat hypotension, when it is clear that the medication has not been successful, is futile therapy using this narrow definition.

The American Thoracic Society statement on withholding and withdrawing therapy defines a life-sustaining therapy as futile if “reasoning and experience indicate that the intervention would be highly unlikely to result in meaningful survival for that patient. Here, meaningful survival specifically refers to quality and duration of survival that would have value to that patient as an individual”(29). This statement exhibits the many difficulties in defining futility; in the absence of explicit statements from the patient, determining the “quality of survival” that is valuable to any patient is a matter of judgment. Furthermore, a major obstacle to decisions based on the concept of medical futility is that, ultimately, physicians cannot predict death or prognosis in any one patient with absolute certainty (30). The best we can provide is an estimate of the probability of survival or treatment effectiveness based on studies in the literature or one's own clinical experience. This does not mean that physicians should be overly preoccupied with uncertainty, thereby ignoring their professional obligation to offer patients and families realistic predictions; Christakis argues that this is a key moral obligation central to medical practice, even if recently ignored in favor of an emphasis on therapeutics (30). Uncertainty contributes to physicians' tendency to delay engaging patients and family members in end-of-life discussions. In addition, family members who are desperately seeking a way to hold on to their loved one may see this uncertainty and hesitancy as a sign that a “miraculous” recovery may still be possible. Because of these difficulties, the concept of medical futility as a strategy for solving the complex debates surrounding appropriate care for terminally ill patients has lost its initial appeal. This strategy, particularly when instituted by health care institutions, may provide some guidance for clinicians, but is unlikely to be the panacea imagined when the futility debates emerged in the early 1990s.

Early and frequent communication between members of the health care team and the family is of paramount importance in reaching decisions to withdraw or withhold life sustaining therapies, particularly if these decisions are motivated by the clinical team's perception that further treatment is futile. When conflicts arise, physicians should make every effort to understand why patients or surrogate decision-makers persist in what is medically perceived to be futile therapy. Do their objections have an emotional overlay such as anger, denial, despair, or guilt? Are there cultural or religious beliefs that influence these decisions? Do decision-makers fully understand the prognosis and likelihood of poor outcomes? Has communication among all parties fostered trustworthiness, or is there a sense of mistrust? Are families and patients getting mixed messages from members of the health care team? Finally, members of institutional ethics committees, as well as religious and community leaders, should be consulted in the resolution of such conflicts.

Many policy makers and clinicians were hopeful that the ethical and legal reforms of the past few decades, translated into concrete bioethics innovations, would go a long way on the journey to improved end-of-life care. However, we suggest that an unexamined demand of the new practices— the requirement that patients embrace the idea that they are dying before making a transition from curative to palliative care—is one reason that the problem of managing death and improving end-of-life care remains unsolved. We became critically aware of the limitations of our clinical bioethics practices governing end-of-life decisions when confronted with California patients from varied ethnocultural backgrounds. The legal and policy reforms of the past decades served this population poorly. An extensive research program examining the challenges of end-of-life care for a diverse patient population has opened our eyes to limitations in the system more broadly (31). We now believe that the implications of our thinking about cultural issues are directly relevant to the care of all patients.

ETHNOCULTURAL DIVERSITY AND CULTURALLY SENSITIVE COMMUNICATION

Throughout this chapter, ethical principles and legal standards governing the withdrawal and withholding of life support have been described. The fact that these bioethics norms embody a Western philosophical viewpoint is rarely pointed out (32). Given the cultural diversity in the United States, physicians are increasingly involved in the care of patients with whom they are not familiar or who do not value the same principles. Given the history of racial discrimination in the United States, others may not trust that standards will be applied impartially when the boundaries between life and death are negotiated. Effective communication with patients and their families requires awareness of one's own values and cultural beliefs and an appreciation of cultural differences (33). In this section, differing cultural perspectives are presented using a case illustration. The case is a composite, drawn from previous research (34) and clinical experience.

Informed consent and informed refusal, which are paramount to respecting patients' rights to self-determination or autonomy, reflect dominant Western values, which privilege the individual. Many cultures, especially Eastern and Asian subcultures, value the family or other broader social unit over the individual. Also, other health care systems may place greater emphasis on the physician's role in protecting the patient from harmful information (beneficence), rather than on the clinician's duty to enable patient decision-making (and enhance autonomy). In a study conducted by Ruhnke et al. (35), Japanese and American physicians and patients were asked to complete a survey assessing their preferences in various end-of-life scenarios. In response to a vignette concerning a cancer patient, 80% of U.S. physicians and only 17% of Japanese physicians felt that the doctor should disclose a cancer diagnosis to a patient. A higher proportion of Japanese patients (42%) felt they should be told of the diagnosis; however, this number was still much lower than that of their American counterparts (81%). The majority of Japanese physicians (80%) and patients (65%) agreed that the doctor should tell the family and allow them to decide whether the patient should be informed. This is in contrast to U.S. physicians (6%) and patients (22%), where a minority chose family-centered decision-making over individual autonomy, although it should be noted that patients endorsed this option more often than physicians. Difference such as these are also found when comparisons are made among U.S. ethnic groups. Blackhall et al. found significant differences in how older Californians valued the concept of autonomy in advance planning for care at the end of life; patients from Korean and Mexican backgrounds gave it less prominence than white or African American elders (36).

In Western biomedicine, “full disclosure” is viewed as essential to the informed decision-making process; however, as illustrated in the Case Example below, not all patients and families value truth-telling equally.

Case Example

Mr. Jeong's cancer symptoms developed in China before he immigrated to the United States with his wife and two sons. Mr. Jeong (a pseudonym) does not speak English, but his older son, who speaks English well, accompanies his father to the clinic and serves as the translator. Since his arrival in the United States, Mr. Jeong has received chemotherapy for his metastatic colon cancer. He also is taking traditional Chinese medicines. The cancer has not been responsive and is rapidly progressing. The health care professionals taking care of Mr. Jeong wish to discuss his preferences for withholding and withdrawing treatments and end-of-life care, including resuscitation choices. On the assumption that the patient must be fully informed of the diagnosis, treatment, and prognosis to make important treatment and end-of-life decisions, they ask his son to translate direct information about his medical condition. The son insists that he should be the one to make these decisions for his father, and that Mr. Jeong would be harmed by the information the clinicians wish him to translate.

What would be required for Mr. Jeong to be truly informed about his diagnosis and prognosis to participate in end-of-life decision making? And more important, to what extent does Mr. Jeong wish to be involved in the decision-making process? By relying on family members instead of a professional interpreter for translation, these questions may not be answered in a straightforward manner. Although the ethical principle of autonomy supports a patient's right to make decisions about care, it does not imply that Mr. Jeong is *required* to make decisions himself. Competent patients should be given the opportunity to make these decisions, but health care workers must accept patient preferences for delegating the responsibility to other members of the family (34).

In conversations with Mr. Jeong's son, an important cultural preference was highlighted: “For us Chinese, we are not used to telling the patient everything, and patients are not used to this either. If you tell them, they can't tolerate it, and they will get sicker.” In fact, the patient's son was quite distressed when he was asked to translate discussions about withdrawal and withholding of treatments. “I did not want to do this, but the doctor found a social worker who speaks Cantonese, and she told my father everything.” When interviewed separately, the oncologist treating Mr. Jeong expressed dissatisfaction with the behavior of the older son: “He came to every visit and was always asking for more chemotherapy for his dad although it was completely unrealistic. He did not allow his dad to express his preferences and he certainly did not wish to discuss end-of-life care.” The end result of this failed communication affected Mr. Jeong dramatically. In response to the straightforward questions

posed by the translator asking if he wished to “limit” therapy, the patient refused to forego resuscitative efforts and asked for further experimental chemotherapy, precluding a referral to the local inpatient hospice where his symptoms could be better managed.

The frustration of the oncologist and the despair of the son are indicative of failed communication as well as differing cultural norms and values. The existing language barrier and absence of “cultural sensitivity” (37,38) were obstacles to effective communication in this case. Cultural sensitivity refers to an awareness of the impact of culture on a patient's values, beliefs, and worldviews. To achieve effective communication and resolve conflicts, physicians and health care workers need to acknowledge these cultural differences, remain nonjudgmental in the face of unfamiliar beliefs, and be willing to negotiate and compromise when differences arise. The reader may notice that this stance is wise in all clinical encounters, a point we endorse.

Table 64-1, based on previous work by Crawley et al. (37,39), reviews general strategies for culturally effective care. These strategies are relevant to all clinical decision making, including discussions about withholding and withdrawing life-sustaining therapies. Additional approaches specific to the end-of-life arena are reviewed by James L. Hallenbeck (see Chapter 47, Cross-Cultural Issues). Appreciation of the cultural diversity in our society today, accompanied by efforts to incorporate cultural sensitivity into day-to-day interactions, determines a good doctor-patient relationship. Needless to say, every relationship is unique and should be tailored to the situation and to the individual. To assume that all patients from a particular culture share similar beliefs and worldviews is to perform a grave disservice to patients. Indeed, stereotyping can be harmful, as well as indicative of disrespect. Cultural awareness serves as a generalized guide; physicians should use open-ended and empathic questions and comments to understand each individual patient's preferences and values.

Identified problems	Strategies
Communication	Be alert for problems, even when patients and physicians share the same language. Check explicitly that patients and physicians have understood each other.
Language barriers	Use trained medical interpreters. When possible, avoid using family or friends to translate.
Caring for specific populations	Increase knowledge of the cultural, economic, and sociopolitical contexts of interactions through guidebooks, community representatives, religious leaders, or professional colleagues.
Conflicting values	Elicit information of patient's or family's explanatory model of illness. Elicit patient's expectations for care. Identify shared values. Be willing to modify own position to reach a mutually acceptable solution. Seek consultation or assistance from other health care workers, institutional ethics committee, or community and religious leaders when necessary.
Mistrust	Respectfully inquire about past or present incidents that might have engendered mistrust. Listen to the patient's story and acknowledge the patient's experience. Address issues that patient identifies as important.
Negative attitudes of providers	Honestly examine your own value system and attitudes toward certain groups; identify and strive to eliminate discriminatory behavior.

TABLE 64-1. STRATEGIES FOR CULTURALLY EFFECTIVE CARE

Mr. Jeong's dilemma can also be attributed to a too-rigid adherence to bioethics norms, as well as to the assumptions underlying those norms. The oncologist was unaware that predicting a patient's imminent death is commonly assumed to bring it about; speaking of one's death is a strong cultural taboo in Chinese society. This may appear ironic in Buddhist societies in which the observant meditate daily about death; however, the *individual's* dying is not the focus of ritual practices (Dr. Craig Janes, *personal communication*, 2001). Mr. Jeong and his son, being recent immigrants, were unfamiliar with the biomedical expectation that patients actively accept that a transition in care is initiated by a patient's active choice. In the course of this transition, curative goals are set aside and palliative ends embraced.

THE DOCTOR-PATIENT RELATIONSHIP

A common theme emerging in our discussion thus far is the importance of effective communication between physicians and patients or their surrogate decision makers. Our values, beliefs, and virtues have an important impact on how we take care of our patients and how successfully we communicate with them. Beauchamp and Childress (40,41) identify four virtues for health care professionals: compassion, trustworthiness, discernment, and integrity. Compassion entails an active concern for the well-being of patients and an empathetic response to their suffering. Honesty and professional competency are necessary to foster a trusting environment. Patients are more likely to trust physicians who take the time to listen and respond to their concerns. The essence of discernment is “the ability to understand what needs to be done for patients, understanding how to do it, and then acting with sensitive and caring responses” (41). The final virtue, and perhaps the most important one, is integrity. Moral integrity is the ability to consistently apply ethical and moral norms to decisions, actions, and behaviors; this virtue should dictate every aspect of the practice of medicine. When patients seek care and medical advice, they entrust their health and often their lives to their physicians and other team members. Faced with such a heavy responsibility, physicians owe it to their patients to be strong advocates of their well-being and to approach each patient with the utmost compassion, professionalism, and integrity. Applying these ideals to end-of-life care presents unique challenges but offers considerable rewards.

Emanuel and Emanuel (42) have put forth four models of the physician-patient relationship: paternalistic, informative, interpretive, and deliberative. In the past century, U.S. medicine has seen the pendulum swing from a paternalistic model, in which physicians acting in the best interests of their patients unhesitatingly dictate therapeutic options, to a more informative model, in which patient autonomy is of paramount importance. The objectives of the informative model are to provide the patient or surrogate decision maker with all the information necessary for informed decision making. In its extreme form, the physician then merely carries out the intervention selected by the patient and does not bias the decision-making process in any way.

Somewhere in between these two extremes lies the essence of a good doctor-patient relationship. In the interpretative model, the physician informs patients and their families of the diagnosis, prognosis, and potential risks and benefits of treatment, but takes this interaction one step further by helping patients articulate their values. The physician can then determine which treatments best realize these values. The final decision is left up to the patient. The deliberative model goes further, allowing the physician to share his or her experience and recommendations with the patient. In this model, physicians suggest therapeutic options that recognize the patient's values, but also guide the decision-making process by suggesting what the patient should do (42,43). Depending on individual circumstances and the characteristics of each patient, the physician may use any one of these models at a given time.

Decisions to withhold or withdraw life-sustaining therapies are inevitably emotionally charged. Ideally, these discussions should be initiated early on as part of the overall goals of therapy, rather than abruptly when all attempts at a “cure” have failed (44). Early consideration allows the competent patient time to determine his or her goals and even encourage family discussions. Palliative care and relief of patient symptoms should be addressed in conjunction with “active” treatment. This also may help diminish the feelings of abandonment that occur when there is a sudden shift of treatment goals from “aggressive” measures to palliative care. Obstacles to this ideal are significant.

PREDICTING AND EMBRACING DEATH: A DILEMMA FOR BIOETHICS

The progress in the technical dimensions of palliative and supportive care highlighted in this textbook is contingent on a set of “decisions” or “choices” made in the course of a patient's uncertain trajectory toward death. Although some argue for and practice “mixed models” of care, in which palliative goals are incorporated into management early in the course of aggressive treatment for cancer or other lifethreatening disease, physicians on the whole do not initiate comprehensive end-of-life care until the patient is defined as “terminal.” Cure remains the clinical focus and the patient's goals and values do not guide decision making; rather, they are often secondary to curative efforts.

Considerable empirical research documents the powerful institutional forces that lead to serious delay in assigning a particular patient the label “dying.” Patients may not be defined as terminal until all imaginable therapeutic options have been tried and shown to fail (45). Similarly, patients one knows well or who are highly engaging may not be defined as in need of palliation, because of the powerful symbolic commitment to cure (45). Emanuel and colleagues have shown that fully one-third of cancer chemotherapy prescribed could be classified as “futile” (46). Most hospice referrals are delayed until the patient is in the last week, or even days, of life (47). Physicians overestimate the likelihood of survival to hospital discharge after resuscitation attempts, estimating that 40% of patients survive when the actual figures range between 10% and 20% (30). The SUPPORT study revealed that “do not resuscitate” orders were not written until the critically ill ICU patients studied were facing imminent death, in spite of an overall prognosis of less than 6 months (5). Callahan calls this “technological brinkmanship”: engaging in active and aggressive treatment until the last moment, and only then pulling back, hoping one has not gone too far in prolonging the dying process (48). Christakis emphasizes how the demands of institutions, as well as characteristics of both physicians and patients, shape professional resistance to predicting death (30).

These observations suggest why end-of-life care remains a significant social and economic challenge. In spite of significant progress in educating health care professionals and the public about the importance of palliative care, powerful countermessages abound. On the one hand patients are exposed to national campaigns to endorse the positive ideal of end-of-life care. On the other hand they are inundated by a different sort of media message. Large, full-scale advertisements seem to suggest that patients need only surf the Internet to find the right clinical trial, the right experimental drug to “cure” them. Cancer centers generally tout their success stories, not their excellent palliative care services.

A further flaw of the “choice” model is the presumption that health care providers offer their patients real and meaningful choices. Given the power differentials separating patients from providers, as well as varied access to medical knowledge, a neutral presentation of information is unlikely. Ethnographic research with cancer patients reveals that “decisions” leading to specific alternatives are often not recognized by patients or acknowledged by physicians. In describing a patient's “decision” to accept recommended surgery, a physician informant stated, “Well, there were decisions but it wasn't like there was any choice involved” (34).

The acceptability of the autonomy paradigm in the clinical arena is not due to its inherent or intuitive acceptance as the “right thing” to do; in fact, it was actively resisted when introduced in the 1970s. The seemingly simple “principlist” approach of much clinical bioethics—autonomy, beneficence, nonmaleficence, and justice—has been accepted in the clinical arena in part because of the profound time compression clinicians face. There is little opportunity for timeconsuming moral reflection in the everyday encounter; when a difficult situation cannot be ignored, clinicians prefer maxims to memorize, rules to apply, and, if at all possible, an algorithm to follow to resolve the situation. Although the autonomy paradigm was initially resisted because of its inherent challenge to professional authority, its procedural approach has been easily adopted as the quick “ethical fix” to the challenges presented by the clinical demands of end-of-life care, symbolized most clearly by the availability of new technologies. In spite of strong critiques of principlism in general, and the over-weighting of autonomy in particular, bioethics practices have been accepted as dogma in the clinical setting (31).

Rather than decision-making algorithms, effective communication among health care providers, patients, and their families is key to the success of compassionate end-of-life care. For certain patient groups this goal is more easily achievable. Cancer patients often have a predictable trajectory, allowing physicians to make accurate predictions about declining health status; such predictions are much harder in end-stage organ disease and the dementias, conditions that account for a significant percentage of mortality. Those with insurance and full access to health care resources are better served by current models of decision making than the poor or disenfranchised. Our analysis of focus groups conducted with African American physicians in four geographic regions of the United States revealed that palliative and end-of-life care are not considered top priority issues (Crawley, *unpublished data*, 2001).

CONCLUSION

Technology and medical therapeutics serve to prolong life and postpone death, at times at the expense of a good quality of life as patients near death. Patients and families are encouraged, in spite of general reluctance, to make decisions about withdrawing and withholding life-sustaining therapies. These decisions occur in highly charged emotional settings in which the strength of the doctor-patient relationship is put to the test. When providing care for patients from diverse cultural backgrounds, the Western emphasis on patient autonomy and active decision making needs to be balanced with the views and cultural beliefs of individual patients. The considerable challenges of caring for patients from societies in which death is not openly embraced point to the limits of abstract decision-making models for all patients, not just those ethnically distant. Current practices create a fiction, the illusion that patients may simply choose *not* to die (31). A more realistic model of care would not require that patients actively embrace death to receive excellent palliative care. Joanne Lynn, among others, promotes a strategy of identifying a narrow range of truly meaningful options that can be built into systems of care, while at the same time structuring a health care system that focuses on excellent practices (e.g., pain and symptom management) that do not need to be “chosen,” that instead become embedded in clinical practice. The “choice points” built into the current bioethics-driven end-of-life practices, in particular the complete fetishizing of decisions about resuscitation, would be a welcome casualty should Lynn's approach be adopted.

We have argued that a focus on discrete individual choices as key signposts on the pathway to death is descriptively invalid, and is resisted by both care providers and patients. It provides only the illusion of control and distracts from needed reforms. Paradigms of clinical care shaped only by utility calculations ignore the existential and unavoidable suffering of the sick and their families. True engagement and open communication is too easily avoided when decision-making is the sole focus. Clinical practices and procedures derived from this model deny the inherent uncertainties of medical treatment; they are based on a false hope that the inevitable failures of the body can be controlled.

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PALLIATIVE CARE AND PHYSICIAN-ASSISTED DEATH

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During the past 10 years, a thoughtful and intense debate regarding physician-assisted death has been occurring. In the United States, the debate has involved the U.S. Supreme Court (1,2), multiple physician, patient, and public surveys (3,4,5,6,7,8 and 9), and many discussions in communities and state legislatures. Broadly, the issues have focused on the morality, ethics, and legality of physician-assisted death. In 1997, the U.S. Supreme Court made a unanimous decision to uphold the right of states to prohibit physician-assisted death. The decision also allows states to permit it (1,2,10,76,77).

For those involved in hospice and palliative care, there are special concerns and challenges related to the issue of physician-assisted death. This chapter will review some of the major ethical arguments, look more specifically at the challenges posed for palliative care professionals, and propose ethically sound clinical strategies for responding to the challenges of a patient's or family member's request for physician-assisted death.

DEFINITIONS

It is important to begin a discussion of physician-assisted death by clearly defining ethical terms used in conversations about end-of-life care treatment options. *Withdrawing or withholding life-sustaining treatment* refers to decisions to stop or not initiate certain medical therapies, with the anticipated outcome that the patient will die from the underlying disease. Common examples include withdrawing a ventilator from a patient in end-stage emphysema, forgoing the use of antibiotics in a patient with terminal cancer and suspected pneumonia, and refusal of tube feeding by a patient with an end-stage neuromuscular disease.

Active euthanasia refers to the direct administration of a lethal agent to the patient by another party with a merciful intent. As commonly practiced today in the Netherlands, this might involve the physician injecting intravenously a quick-acting sedative followed by a paralytic agent to halt respiration. Active euthanasia may be voluntary, involuntary, or nonvoluntary, depending on whether the patient has freely chosen it, has freely rejected it, or has offered no opinion. This chapter considers only *voluntary active euthanasia* because that is the only form being seriously advocated in the United States today.

Assisted suicide refers to the patient intentionally and willfully ending his or her own life with the assistance of another party. This assistance may include different levels of involvement—merely providing information about how to commit suicide, providing the means to commit suicide, such as a lethal quantity of pills, or actively participating in the suicide, such as being present at the scene and inserting an intravenous line through which the patient may then administer a lethal dose (11). The widely publicized actions of Dr. Timothy Quill (12) and Dr. Jack Kevorkian (13,14) provide examples of the second and third levels of involvement, respectively.

For this chapter, *assisted death* refers jointly to the practices of voluntary active euthanasia and assisted suicide. Most of the ethics literature has focused on the special problems of the physician's role, that is, the practice of *physician-assisted death*. In a hospice context, the roles of the other health professionals and the family are extremely important and, in some cases, the patient may request assistance in dying from one or more of them as well as (or instead of) from the physician.

It is also important to be clear about what is *not* assisted death. As noted, it is *not* an assisted death if a competent person decides not to initiate a specific therapy (e.g., further chemotherapy, antibiotics for a pneumonia or another septic process, renal dialysis, or artificial nutrition or hydration). It is not an assisted death to withdraw any of these options from the terminal patient. The use of high-dose opioids when the intent is to relieve pain and not to hasten death is *not* physician-asssted death. Although many still believe that high-dose opioids pose a serious risk of fatal respiratory depression, palliative specialists know that this very seldom occurs with proper titration of analgesic doses, even when very large doses of opioids are administered in terminal illness. (15,16). Even if respiratory depression is a foreseen (but unintended) consequence of adequate analgesia, administering the analgesic is not considered to be physician-assisted death.

Withholding and withdrawing life-sustaining treatment is widely accepted today both in ethics and law as appropriate and compassionate care. This clinical practice is ethically and legally acceptable only when the competent patient is fully informed and freely chooses this option or has clearly documented these choices in an advance care plan document. Some, notably Rachels and Dixon (16,17), have argued that there is no morally relevant difference between this practice and the practice of assisted death. Dixon argues that fairness requires that if we legalize physician-assisted death, we should also make active euthanasia legally available (17). In this chapter, without giving detailed arguments, I will assume that if assisted death can be justified, it must be justified on its own merits and not merely because it shares some ethical features with the relatively uncontroversial practice of withdrawing or withholding life-sustaining treatment (18,19,20 and 21).

ETHICAL ARGUMENTS

Patient Integrity

Patients who are living with a life-limiting disease want their personal values and goals maintained and respected. For many patients, the most important personal values are autonomy and personal integrity. From the patient's perspective, this means that one's belief system, personal values, and life goals will be honored and respected and that they will play a vital role in treatment plans and palliative care planning. Most patients have the expectation that their suffering will be moderated, their pain will be controlled, and they will have the opportunity to have meaningful discussions with their physicians and family concerning the type and extent of their treatments (9,10,22,23 and 24). A recent report of the Oregon Health Division (36,77) confirms that 67% of the 26 persons who experienced a physicianassisted death in 1999 identified loss of autonomy, an inability to participate in activities that would make life meaningful, and loss of control of bodily functions as reasons for seeking an assisted death.

Proponents of assisted death would argue that they are honoring the personal integrity and personal autonomy of the person by being willing to discuss and assist the patient with *all* treatment/care choices for the patient, including assisted death. Proponents also claim that physician-assisted death minimizes harm to the patient and others. They argue that the patient should determine what counts as harm and may legitimately decide that ongoing life with severe suffering is a greater harm than a painless death (25,26).

Opponents claim that however important the moral value of patient autonomy, it is insufficient to justify the practice of assisted death (10,17,18,27,28,29 and 30). Autonomy may justify withdrawing or withholding treatment because that constitutes a negative right of noninterference, which is strongly grounded in the concept of respecting personal bodily integrity. But it cannot justify a positive right to demand that others take specific actions to promote one's own idea of one's welfare—especially when those actions cause death. Some opponents also make the claim that causing a death is one of the greatest harms that a clinician could inflict on a patient. The basic principle of “do no harm” should be understood as requiring a healing relationship between the physician and the patient and, thus, is in

direct conflict with respect for patient autonomy when assistance in dying is requested.

Compassionate Response to Suffering

For some physicians, a request by a patient for death assistance is viewed as a plea to release the patient from intolerable suffering. From this perspective, such assistance is understood as an act of compassion. Quill and others (31,32 and 33,40) have argued that a willingness to discuss this option with the patient often may act as a suicide preventive because once the patient's concerns and fears have been fully discussed, the physician may be able to propose alternative means of relieving suffering short of death (8,10,34,35 and 36). By contrast, if physicians refuse to offer assistance, suffering patients may avoid these searching conversations and instead commit suicide in a manner that actually increases their own and their family's suffering.

It is a serious mistake to equate suffering narrowly with pain and other unpleasant physical symptoms. Suffering is defined through the experiences of the individual, which includes a personal sense of impaired quality of life, and is understood as a fundamental threat to one's wholeness as a person. Suffering is ultimately tied to one's personal belief system. It reflects how those beliefs define the reality of the human person and how one experiences an illness in the overall context of one's life journey and personal expectations for the future. Two patients may report similar symptoms but have vastly different experiences of suffering (35,37,38,39 and 40,70).

Proponents of assisted death point to the multifaceted and complex nature of suffering as a defense for the individual's right to choose a quicker death because no one can really comprehend the severity of anyone's suffering. The challenge for those who provide palliative care and hospice care is to develop a plan which applies the breadth and depth of palliative care, that is, to attend to the physical, emotional, and spiritual needs of patients and their families within the context of each patient's belief/value system. We are faced with unique challenges when a patient has seemingly lost all hope for relief of his or her suffering. Although excellent palliative care and hospice care should greatly reduce the number of patients who may request death assistance, it would not negate the need for this option in some cases.

By contrast, opponents claim that proponents have a shortsighted and simplistic approach to the relief of suffering. Precisely because suffering is multifaceted and intimately tied to personal meaning, there are numerous options to offer suffering individuals to assist them in restoring a sense of meaning in their lives. To relieve suffering by eliminating the sufferer must always be viewed as an inadequate response. Attending adequately to loneliness, fear of death, depression, unresolved conflicts, lack of forgiveness, anger, and hopelessness is harder work but ultimately will allow a better personal resolution. This is especially important because physicians and families may tend to project their own suffering onto the patient and therefore conclude that a premature death is actually the merciful choice from the patient's perspective (8,10,40,41).

Safeguards

Both proponents and opponents of physician-assisted death agree that safeguards are needed to protect the patient's safety and integrity and to protect society from physicians who might abuse the end-of-life choice (10,25,30,31,42,43). Table 65-1 lists some commonly proposed safeguards and guidelines for discussing the choice of assisted death (31,42).

The patient must have a condition that is incurable (not necessarily terminal) and is associated with severe suffering without hope of relief.
All reasonable, comfort-oriented measures must have been considered or tried.
The patient must express a clear and repeated request to die that is not coerced (e.g., emotionally or financially).
The physician must ensure that the patient's judgment is not distorted—that is, the patient is competent to make a rational treatment choice.
Physician-assisted death must be carried out only in the context of a meaningful physician-patient relationship.
Consultation must be obtained from another physician to ensure that the patient's request is rational and voluntary.
There must be clear documentation that the previous six steps have been taken and a system of reporting, reviewing, and studying such deaths must be established.

From Quill T, Cassel C, Meier D. Care of the hopelessly ill—proposed clinical criteria for physician-assisted suicide. (Sounding Board) *N Engl J Med* 1992;327:1380; and Miller F, Quill T, Brody H, et al. Regulating physician-assisted death. *N Engl J Med* 1994;331:119, with permission.

TABLE 65-1. SAFEGUARDS AND GUIDELINES FOR THE DISCUSSION OF ASSISTED DEATH

As previously discussed (see the section Compassionate Response to Suffering), proponents believe that patients are the best judge of their own suffering and should have the option of discussing their situation with their personal physicians and developing a mutually agreeable plan for control of their pain and suffering (71). Proponents also believe that repeated and compassionate conversations between the patient and the primary physician over time will build the trust and rapport necessary for honest and uncoerced conversations among the patient, physician, and family members. Many proponents also believe that consultation with at least one other physician is a vital safeguard. A parallel safeguard is the assurance of accurate and clear documentation that all of the guidelines have been followed.

Most opponents would agree that patients are the best judge of their own suffering and that all reasonable comfort measures should be considered and tried. They would agree that the more open and frank discussions between the physician and the patient should occur on topics such as pain control and the patient's perception and experiences of suffering. In the opponents' opinion, these types of discussions and the subsequent individualized plan of care for the patient would negate the need for the option of assisted death. Opponents see the potential for coercion as very real and often quite difficult to ascertain so that the proposed guidelines would be inadequate in practice. Opponents are also concerned about the erosion of the physician-patient relationship occurring when physicians start providing the means of death for their patients. They see flaws in the consultation and documentation guidelines. They think that a physician could and would choose another physician of like mind to serve as consultant and are skeptical that any documentation system could assure consistency and compassion among physicians and guarantee safety and sensitivity for patients (10). Proponents are encouraged by the processes, documentation, and safeguards developed in Oregon (36).

Professional Integrity

Opponents of physician-assisted death often argue that causing death is inconsistent with the moral integrity of the physician, who should always strive to be a healer and never a killer (62). In this view, even if society deemed it appropriate to permit assistance in dying, ethical physicians would be obligated to refuse to provide such assistance. Some other group of professionals or technicians would have to be appointed by society for that role (44,45). Similar arguments of integrity have been made on behalf of nurses, pharmacists, and other health care professionals (29,46,47,48 and 49).

Some proponents of physician-assisted death claim that the opponents rely on too narrow a conception of the moral goals of medicine. Healing in the usual sense, they claim, is but one of the goals that define the content of the physician's professional integrity. Relief of suffering, respect for the patient's voluntary choices, and aiding patients to achieve the most peaceful and dignified death possible are also worthy aims. Therefore, suffering that has been unrelieved by excellent palliative care in a patient who has made repeated voluntary requests for death assistance would constitute an exception to the general prohibition. In such narrowly defined cases, a physician could assist death while maintaining ethical integrity (so long as assisting death did not violate any of that physician's personal ethical, moral, or religious values) (50).

Slippery Slope

Concern about a “slippery slope” is one of the main arguments raised by opponents. They contend that once the legal barriers to physician-assisted death are broken, there will be little justification for limiting this practice to only the terminally ill. What is today an *option* to choose assisted death might become an *obligation* to choose it, especially under pressures of cost containment and biases toward vulnerable populations such as the aged, the HIV positive and persons living with AIDS, minorities, and the disabled (51).

In particular, Miles (41) has raised the concern that vulnerable populations will be subtly pressured into choosing death by messages that they are not worth saving. Many family members and physicians who care for persons with chronic illnesses may become exhausted and exasperated and therefore might be driven to go along with or even encourage the suicide request.

Proponents respond that proper attention to safeguards will prevent many problems and concerns raised by the “slippery-slope” argument. Typical of the dispute between proponents and opponents of assisted death are sharply divergent interpretations of the current debate and discussion of the Oregon statutes and experiences. One side argues that this is the manifestation of our worst fears regarding physician-assisted death (10,30,35). The other suggests that published reports from the public health department in Oregon confirm that the safeguards are working, palliative care and hospice care have markedly increased, and in reality very few

patients over the past 2 years have requested and carried out an assisted death (36).

Substituted Judgment

Opponents worry that society will extend physicianassisted death to incompetent patients. Most proposals for physician-assisted death in the United States today specifically exclude the option of choosing physician-assisted death by an advance directive. The slippery-slope argument, however, claims that this barrier will become impossible to maintain once physician-assisted death is legally permitted (20,51). In 1997, the U.S. Supreme Court made a unanimous decision to uphold the right of states to prohibit physician-assisted suicide (10). The debate was not ended by this decision. It moved into the arena of state debates and referenda (10,52,53,54 and 55).

IMPLICATIONS FOR PALLIATIVE CARE AND HOSPICE

Official Policies

Both the National Hospice and Palliative Care Organization (NHPCO) and the American Academy of Hospice and Palliative Medicine have position statements opposing the legalization of assisted death (56,57). The American Academy of Hospice and Palliative Medicine statement is brief and states that competent palliative care usually relieves the pain and suffering of terminally ill persons and their families. This statement calls for policy reforms to ensure comprehensive hospice services for all. The NHPCO position paper (Table 65-2) is considerably more detailed and reviews all of the major points discussed. In summary, the NHPCO statement maintains that allowing unpreventable death to occur with dignity and comfort is quite different from accepting death as an expeditious way out of difficult situations for individuals or society.

In November 1990, a resolution was adopted rejecting the practice of voluntary euthanasia and assisted suicide.
These practices are counter to the National Hospice and Palliative Care Organization's core principles of relief of suffering, coordination of palliative and support services for the patient and family, a focus in maintaining the quality of remaining life, and a commitment to affirm life and neither hasten nor postpone death.
Hospice offers competent, appropriate, and compassionate palliative care to patients and their families as an effective choice for the care of dying patients and their families.
Aggressive palliative care can improve the quality and quantity of remaining life, as defined by the patient's life goals and choices.
Patients and their families need to be given the opportunity to discuss the accuracy, prognosis, and range of palliative treatment options appropriate for their personal situation and lifestyle.
The administrative and financial requirements of developing and maintaining assisted death as a component of the health care delivery system could competitively diminish the support needed to increase access to appropriate palliative care.

From Statement opposing the legalization of euthanasia and assisted suicide. Arlington, VA: National Hospice and Palliative Care Organization, with permission.

TABLE 65-2. MAJOR POINTS OF THE NATIONAL HOSPICE AND PALLIATIVE CARE ORGANIZATION'S POSITION STATEMENT ON ASSISTED DEATH

Both organizations see hospice as an ethically sound model of compassionate, cost-effective, patient- and familyoriented care. They also would argue that hospice care should be available to all and affordable for all who would opt for palliative care, and that all health care professionals should possess basic knowledge of palliative care and hospice management principles.

Attitudes

As one might expect from official policy statements, there is a marked difference in attitudes toward physician-assisted death among hospice workers in general. A slight majority of physicians in the states of Washington and Michigan favor a policy that would permit the option of physicianassisted death; other surveys have shown that from 33% to 40% of physicians favor such a policy (3,58,59). By contrast, surveys of hospice physicians, nurses, and volunteers show only a minority in favor of allowing physician-assisted death, and about two-thirds strongly opposed to it (29,61).

It is natural for those who devote so much of their energy to relief of symptoms and who see the vast majority of their patients “living well until they die” to view the occasional patient who chooses physician-assisted death as either a failure or a threat. Some of these patients may have had prior exposure to hospice, and the current decision for assisted death can be experienced as a rejection of the hospice philosophy. Even patients who had never experienced organized palliative care may seem to be saying by choosing assisted death that they do not value what is offered by palliative care. So, there are understandable philosophical and emotional reasons for hospice caregivers to react negatively to physician-assisted death.

Hospice professionals' approach to care of the terminally ill and dying emphasizes that each person will be supported through a variety of personal and professional resources to live well and be well supported in his or her death experience. At first glance, physician-assisted death would seem to be inappropriate, unnecessary, or both in every case (51). The philosophy of some hospice professionals is consistent with the views of proponents of assisted death. Both have in common a rejection of the dominant mode of dying that seems to characterize the American hospital setting—a death prolonged by excessive use of technology inadequately attended by concern for amelioration of symptoms and a depersonalized and deindividualized death, as patients' true choices are routinely ignored and human relationships and human caring are given short shrift in a world of machines. Both hospice professionals and assisteddeath advocates agree that there are much better ways to die and that the direction lies in more appreciation of human needs and of individual choices and values. Most hospice professionals would disagree with assisted-death advocates, however, by choosing improvements in the approach to caring for the dying in contrast to advocating for assisteddeath methods.

Success of Palliative Care

Advocates of physician-assisted death assume that palliative care modalities, while normally highly successful, cannot work in 100% of patients. There will of necessity be a few patients whose unpleasant symptoms, personal suffering, or inability to achieve personal needs or goals will not be ameliorated by even the most highly skilled palliative interventions. Many advocates of physician-assisted death would favor restricting the option of assisted death to that small percentage of patients who cannot be assisted effectively by palliative care treatments. This suggestion angers some palliative care specialists who contend that their treatment modalities are much more effective than physician-assisted death advocates appreciate. Knowing full well how often the average U.S. health professional underestimates the effectiveness of quality patient-centered palliative technology—and how often a so-called failure of palliative care is the result of an untrained practitioner either undertreating or choosing suboptimal treatment strategies—palliative care specialists may confidently predict that if they could only offer all needy patients in the United States the best quality hospice care, then the demand for physicianassisted death would soon be nil (55,56,73,74 and 75).

But both well-designed studies and common sense would lead to the conclusion that no medical therapy, however marvelous, can always succeed (33,59). Thus challenged, palliative care specialists sometimes suggest that they can indeed effectively treat all terminal patients with distressing symptoms. Even the 3–5% or so of patients whose physical suffering does not respond well to current treatment options and modalities (traditional and complementary) can be offered terminal sedation (59,72). Because the intent is to relieve symptoms and not to shorten life, pharmacologically induced coma does not constitute physician-assisted death but instead is an acceptable, if extreme, use of palliative treatment options (60).

Defenders of physician-assisted death have offered two rebuttals to this argument. First, they have argued that in many instances in which pharmacologically induced coma might be used, death follows so surely and within so short a span of time that it is a semantic quibble not to view this as physician-assisted death from a *moral point of view* (while recognizing of course that from a *legal point of view,* sedation to the point of coma is quite acceptable even in jurisdictions where physician-assisted death would be a crime).

To understand these ethical and legal nuances, it is important to discuss the application of the ethical principle of double effect to high-dose opioids for analgesia and to pharmacologically induced coma. To opponents of physicianassisted death, the two instances are quite analogous. In both cases, one intends relief of symptoms, not death. One foresees the risk that the means used to relieve symptoms could cause a hastened death, but hastening death is not one's true intent. Thus, death is a foreseen but unintended consequence of an action that is ethically defensible, and so the use of that means is ethically justified despite the risk.

To proponents of physician-assisted death, however, the two cases are quite different. Very few patients actually suffer respiratory depression from properly administered opioids in terminal illness. By contrast, in most instances of pharmacologically induced coma (most commonly with barbiturates), death follows with near certainty and within a much shorter period. Moreover, if one sees respirations being depressed, one would not lower the dose because the patient's awakening would mean the cruel reinfliction of the intolerable suffering that one sought to avoid by inducing the coma in the first place. More to the point, the question of intent is more

clouded in the case of induced coma. The fact that one elects to use this extreme measure, which often results in death within days or even hours, means that one has decided that any prolongation of conscious life is incompatible with this patient's true interests. If, by chance, the coma persists for many days or weeks, the palliative care professional will seldom regard this as a good outcome. Indeed, this may make the death an even more poignant tragedy for the family as well as for the caregivers.

A second rebuttal is that some terminally ill patients who have demanded the right to physician-assisted death have claimed that a drug-induced coma typifies the loss of control and dignity that it is their overriding goal to avoid. For at least this small group of patients, palliative care experts might relive unpleasant physical symptoms but only at the cost of violating the patient's own deeply held values regarding quality of life.

Pain versus Suffering

Suffering is a much broader concept than is pain or any set of unpleasant symptoms. The best available study of patient attitudes in a setting where physician-assisted death is openly practiced and legally tolerated reveals that only about 10% of patients requesting euthanasia suffer principally from pain and only about 50% suffer from any physical symptoms of the sort that can be easily relieved by palliative medical interventions. A significant number of requests to die arose from those who state that they are merely tired of life or whose general level of functioning has deteriorated below their personally acceptable minimum (60,77). Recently published reports from Oregon states that the most common reasons for asking for assisted death include loss of autonomy, loss of control of bodily functions, an inability to participate in activities that make life enjoyable, and a determination to control the manner of death (36,77). A recent study, which examined physician attitudes regarding physician-assisted suicide and AIDS patients, revealed that 48% of the physicians would assist the patient in the survey's case scenario and 53% had positively responded to a patient request in their own practices.

Possibly many or even most patients would be aided by emotional and/or spiritual counseling to the point where they would no longer request assisted death. A more sensitive and patient-centered approach, including the use of spiritual histories, would assist the hospice professional and the patient to gain a deeper understanding of the meaning that the patient attaches to his or her individual circumstances and not merely the assumption that palliative care treatments have been underused (22,24,28,60).

Funding for Palliative Care

One recurring argument against allowing physician-assisted death is that hospice and palliative care have been historically underfunded in the United States. According to this argument, as soon as physician-assisted death is a legal option, patients will be steered toward a quick, painless, cheap death and will be discouraged from seeking potentially expensive hospice care. The net result will be the serious underfunding of all types of palliative care programs, and the option to choose palliative care will be an option on paper only for most U.S. patients. Many U.S. hospice professionals charge that palliative care has been very slow to develop in the Netherlands and that country's euthanasia policy is directly to blame. Hospice professionals have experienced the problems and challenges of chronic underfunding and of working with physicians and administrators who were often ill-informed about hospice care. Understandably, they are skeptical of any proposal that assumes that palliative care has arrived and that adequate funding is on the horizon (61).

Defenders of the assisted-death option have argued in reply that a properly regulated and legalized option for physicianassisted death could actually support the expansion of hospice. The recent report on the Oregon experience with physicianassisted death would support this argument (36,77).

Many such proposals include the stipulation that no patient will be granted the request to die until palliative care experts have concluded that the patient cannot be effectively helped by appropriate treatments. In effect, the proposals would require that every patient requesting physicianassisted death undergo a trial of palliative care (31,42). Proponents further assume that in the vast majority of cases, the patients would be so impressed with the success of the treatment that they would elect to remain in the hospice program rather than be put to death. The result, they argue, will be additional political support for hospice programs and for palliative care training and research, such as the American Medical Association's Education for Physicians on End-of-Life Care program (48).

It is possible, of course, that health care professionals might merely rubber-stamp requests for assisted death rather than engage in detailed conversations with their patients. Ironically, this outcome would be more likely if the nation moves toward legalizing physician-assisted death and if (as opinion polls now suggest) the best trained palliative care specialists refuse as a matter of conscience to have anything to do with the assisted-death program, even to the extent of screening patients and consulting on available palliative care alternatives (29,61).

CLINICAL MANAGEMENT OF REQUESTS FOR ASSISTED DEATH

Although the debate between opponents and proponents of assisted death is complex and apparently intractable, many aspects of the practical management of patients who request direct assistance in dying will be the same regardless of the clinician's moral or ethical stance. There are clinical approaches that should fit both ethical positions comfortably. A few areas of practice must differ, however, to remain consistent with the clinician's own ethical or moral commitments (Table 65-3).

The clinician should listen to the request for assisted death in an open and sympathetic manner and evaluate the issues underlying the request.
The clinician should share her personal stance with the patient in an open and professional manner, always assuring the patient that he will be supported throughout the experience of his personal decision-making process.
All clinicians should take appropriate steps to process their personal emotional reactions to the patient's request, e.g., hospice team meetings.
The clinician should have a continuing dialog with the patient and appropriate family members or support persons concerning the development and implementation of therapeutic treatment plans, including a request for assisted death, in a manner consistent with the clinician's ethical values and personal belief system.

From Miller F, Quill T, Brody H, et al. Regulating physician-assisted death. *N Engl J Med* 1994;331:119, with permission.

TABLE 65-3. SUGGESTED STEPS FOR THE CLINICAL MANAGEMENT OF A REQUEST FOR ASSISTED DEATH

Reactions to Patient Request

As noted above (see the section Attitudes), a hospice patient who requests physician-assisted death may well trigger intensely negative emotional reactions among members of the care team. It is very important that those emotional reactions be validated by other team members but not be allowed to derail the necessary conversations with the patient that will support the patient's values and choices, as well as assess future care needs. Ideally, the patient's request will be received sympathetically but matter-of-factly. The patient may be told that he or she is hardly alone among patients facing death in making such a request and that the clinician very much appreciates the trust shown by the patient in stating the request openly. The clinician would then continue the dialog with the patient regarding underlying reasons for this request and come to mutual agreement that this request will be discussed at his or her next care meeting.

Alternatively, a patient may confide this request or the fact that she is seriously considering suicide to only one member of the palliative care team with whom she may experience a deeper personal trust. In that event, the team member ought initially to respect the confidence but state that he or she feels a very strong obligation to share that information with all other team members so that as a team they can discuss how best to offer future assistance to the patient. The clinician should persist in seeking the patient's permission to share the disclosure with the rest of the team members. If the selective disclosure indicates that there are unresolved issues of distrust between the patient and other team members, the most therapeutic approach may be to address those issues head-on as part of the negotiations about the disclosure. If the patient continues to refuse permission to share this information, then the clinician is faced with the very difficult conflict about when it is justifiable to violate a patient's confidence (64). One must balance the goal of preventing harm to the patient against the possibility that violating a confidence (or threatening to do so) may lead to even less disclosure of key information and therefore a lessened opportunity to help the patient in the future.

If the clinician on balance thinks that the secret ought to be revealed to colleagues, the justification would be that the clinician is at the patient's bedside not as a solo practitioner but as a representative of the team, and not to allow the team to function cohesively is in a sense to reject the clinician's care. This justification will be most plausible when the team aspects of care and the sharing of information in the team have been fully disclosed to the patient as a part of the admission process. Also, in order to minimize further loss of trust, the clinician who feels obligated to reveal secret information should frankly inform the patient of this and the reasons for

disclosure.

Some requests for death assistance are transparently a result of a temporary stressor mood change and are very unlikely to represent the considered, enduring posture of the patient. The clinician may deal with such requests by validating the emotional state of the patient and responding with appropriate brief counseling.

All patients should be informed at this stage that it is the practice of the team to take all requests for death assistance very seriously. The patient should be informed that it is the experience of the team that the concerns and problems that prompt such requests can usually be ameliorated once the team has carefully assessed the patient's situation and further care options. The clinician should promise speedy attention to the concerns that the patient raises and full communication of the team's planning processes.

At this point in the inquiry, the clinician or the organization will take different approaches depending on their moral/ethical position on physician-assisted death. A clinician (or team) who is morally opposed to this practice in all cases should share this information with the patient lest the patient entertain unrealistic hopes of later assistance. The statement of refusal to consider the option of assisted death should be coupled with the promise to stand by the patient until the moment of death and to continue to search exhaustively for any means other than death assistance to ameliorate the patient's suffering. The clinician may wish to add that a moral distaste for the action of assisting death does not equate with a moral condemnation of the suffering individual who is making the request.

The clinician (or team) who is morally/ethically willing to consider the permissibility of assisting a patient's death in carefully selected cases may at this point share that stance with the patient. The clinician should next point out the procedure the team has agreed to following to be sure that the patient is making a voluntary, considered choice and is suffering in ways that cannot be relieved by any other means. The estimated amount of time needed for this determination, and to consider and suggest alternatives, should be shared with the patient. In any event, the patient needs to be told that no quick and easy acquiescence is contemplated. The clinician may wish to inform the patient of the statistical chances that the patient will select an alternative means of addressing his suffering and will in that event no longer request a quick death.

Possible Scenarios

After this initial discussion around the patient's first request for assisted death, the palliative care team should engage in a careful inquiry to determine the nature and origin of the patient's suffering, taking at face value that if the patient was prompted to ask to die the suffering must be more severe than the team had previously appreciated. The inquiry will be aided by understanding some common scenarios observed among patients making such requests (63). The categories developed by Quill are very useful (33,34); the following six scenarios illustrate situations in which all observers agree that the best option lies not in assisting death but in providing some other type of care.

Inadequately Treated Physical Symptoms

The easiest category to deal with is the patient who seeks death because of suffering caused by inadequately treated physical symptoms. The palliative care team may have missed the onset, duration, or severity of a symptom. The patient may have felt compelled for a variety of emotional reasons to deny or minimize the symptom. Or, a previously prescribed treatment may be producing unpleasant or intolerable side effects that the patient similarly feels obligated to deny or minimize, possibly to avoid hurting the feelings of the clinicians. In any case, a searching discussion in which physical symptoms and treatment side effects are explicitly explored should reveal the source of the problem, or other family members may be able to enlighten the hospice team on the nature of the complaint. A trial of an improved treatment strategy to show the patient that the troublesome symptom can be relieved to tolerable levels will also be successful in helping the patient experience and believe that his or her symptoms are able to be relieved.

Depression

Untreated depression can cause a patient to wish to die and to consider the future hopeless. A team member skilled in the differential diagnosis of depression should interview the patient with this possibility in mind. In an elderly patient, special expertise in geropsychiatry may be required both to distinguish the signs of depression from the side effects of aging or chronic illness and to determine a type and dose of antidepressant medication that can be successfully and safely administered to the patient (64,65).

The diagnosis of depression does not necessarily lead to the successful treatment of depression soon enough to preserve the terminal patient's quality of life. Thus, it is of no benefit to label him or her as depressed. As always in palliative care, the treatment of depression in the terminal patient should be aimed at the actual relief of troublesome symptoms rather than cure of a disease. This may require flexibility and creativity in combining medication with emotional support.

Family Dysfunction or Conflict

A patient's wish to die may grow out of conflict within a troubled family relationship. A patient may wish to die because of a fear that painful and dissatisfying family relationships are not going to improve. In other cases, a request may be a manipulative counteroffensive aimed at punishing other family members. Most hospice teams have social workers and chaplains as well as family practice physicians and nurses who are capable of evaluating family dysfunction and developing an appropriate management plan.

Spiritual Crisis

A request for assisted death may signal the fact that whatever belief system that previously provided the patient with a sense of meaning in his or her life is no longer experienced as supportive or meaningful, and the patient now feels that further existence would be without meaning. It may also suggest that this patient had been able to cope with previous life stressors without invoking any spiritual belief system and is now belatedly confronting the fact that he or she has no such resource to draw upon in looking at impending death.

Spiritual counseling may help to resolve the crisis and to restore a sense of meaning to the patient's life in the context of the illness and impending death. To be effective, the counseling will have to be tailored to the patient's beliefs and current needs. A careful assessment of the patient's sense of the nature of the current conflict and of why previously helpful spiritual or emotional supports no longer seem to be working is essential for identifying the type of counselor who would be most helpful. Human beings often assign meaning to events through the construction of narrative. Engaging the patient in telling or writing stories about his or her past life or present illness or about hopes for his survivors may facilitate the process of restoring hope and meaning (22,28,37,56,60,66,67).

Unremitting Suffering Despite Adequate Support

This category, which with high-quality palliative care will include relatively few patients, presents the starkest contrast between those morally opposed to and morally accepting of physician-assisted death. It is the patient who has failed to achieve adequate relief of suffering through appropriate trials of palliative treatments, with proper attention to emotional, social, and spiritual factors, and the patient who has been shown to be competent and persists in requesting death who presents a major ethical challenge to most palliative care clinicians. Supporters of physician-assisted death would argue that it is precisely this setting in which we as a society should support assisted death (63).

A problem will arise for the clinician opposing physician-assisted death if the patient has refused to try an offered mode of therapy or has ceased treatment before full therapeutic benefit occurred because of unpleasant side effects or fear of them. In some cases, the clinician will judge that the side effects were truly severe and debilitating or that their likelihood of occurring was exactly as the patient predicted. In such cases, the clinician might in good conscience proceed to assist death. But, in other cases, the clinician may judge, fairly or unfairly, that the patient's reasons for refusing the offered therapy were inadequate or insubstantial and that in effect the patient was so intent on receiving assistance with death that he was not really trying to achieve relief of suffering by any other route. This presents a serious dilemma for supporters of physician-assisted death. It is evident, however, that only patients can truly know how much they are suffering and that judgments by third parties that their reasons for refusing an offered therapy are flawed or inadequate seem to undermine the respect for free choice that motivated support for assisted-death policies in the first place. On the other hand, if patients may receive assistance in dying after refusing all offered therapies for any reason whatsoever, then we have in fact created a policy of death on demand in which all so-called medical safeguards are spurious.

It is important for clinicians to recall in such cases that it is much harder to make the case that assistance in dying is a *right* of the terminally ill patient than that such death assistance is *permissible* in rare, selected circumstances. If patients have no moral right to death assistance, then physicians can refuse to assist death in all dubious cases. This effectively places the burden of proof on the patient rather than on the physician—a negative situation if one adopts a strongly libertarian posture but a positive one if one is concerned about the ease with which any policy of assisted death may be abused to the detriment of vulnerable persons.

Those morally opposed to assisted death who are facing patients with unremitting suffering will again wish to affirm their commitment not to abandon patients and to always stand by them in their suffering while continuing to try new approaches and new combinations of treatments despite the waning likelihood of success. Spiritual counseling becomes critically important at this juncture because even patients who may continue to have some suffering before death may be helped to attach new and profound meanings to that suffering so that the suffering becomes personally more bearable. If heavy sedation or induced coma has not previously been considered, they should be reviewed with the patient and the family at this time. Knowing that these treatments and spiritual and emotional supports are available may help the patient find the strength to endure.

Hastening Death by Withdrawing Nutrition and Hydration

A policy proposal (65) and case report (69) awakened interest in a legally permissible strategy allowing patients to hasten death, even in jurisdictions proscribing physicianassisted suicide. The patient refused to eat and drink and the physician provided palliative support to prevent any discomfort of dying by dehydration. Clinicians may legitimately differ over the moral assessment of this practice. For some, it will seem a clear-cut case of providing compassionate symptom relief while patients exercise their legal and ethical right to refuse medical interventions, including artificial nutrition and hydration. For others, it will seem an obvious subterfuge in which one stays on the right side of the law while engaging in an act that is morally indistinguishable from physician-assisted suicide. After all, the patient refuses artificial nutrition and hydration not because of an inability to drink or eat in the regular manner and not because artificial administration is excessively painful or burdensome but because the patient has determined that future life is not worth living and that an early death is preferable. Thus, such cases are easily distinguishable from the more usual hospice case in which symptom relief is offered and artificial nutrition and hydration are seldom used because they would add no comfort and merely prolong the dying process.

Palliative care professionals and organizations may be divided on this strategy. Some who favor physician-assisted death will regard prolonged death from dehydration, even if symptoms are well controlled, as an undignified travesty of what could otherwise have been a quick and painless death had more direct means been used. However, some physicians who advocate physician-assisted death but fear the legal repercussions may find this an acceptable temporary solution. In that event, they could mention it as an option to patients who repeatedly request assistance in dying and whose suffering has not been adequately relieved by other means.

Considerable patient and family education is helpful and necessary because few health professionals and laypersons are aware that such a death can be relatively painless and comfortable (22,68,69). Some patients or families may still find the prospect unacceptable even after several conversations. For those patients who might elect to use this method, it will be important to allow for changes of heart along the way as well as to provide the promised symptom relief promptly and adequately throughout the process.

CONCLUSIONS

The foregoing sections have explained the ethical (moral) issues, the professional implications for hospice professionals, and the clinical management of requests for assisted death from hospice patients. Commentators on these issues (10,22,31) emphasize that there needs to be a stepwise approach to requests for assisted death, which should include assessment of decision-making capacity and lack of depression, excellent discussions regarding advance care planning, evaluation for treatable causes of symptoms and treatment if possible, proper utilization of professional resources (including spiritual), a network of caring (both family and professionals), and a death that expresses personal dignity and values (10).

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PALLIATIVE CARE:ETHICS AND THE LAW

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Practitioners of palliative care face both legal and ethical imperatives. Those two realms usually overlap reasonably well because law is, at its base, a consensus on ethics of the place and time (1). There is tension—the laws may lag the ethics, and sometimes ethics lag law. At any given time some will feel that the law goes too far to impose an ethic, while others are impatient for it to do more. However, these tensions tend to exist at the edges and not at the core of law or ethics.

Lawyers and ethicists approach some issues differently and therefore reach somewhat different conclusions. Most important, perhaps, law varies from state to state. Ethics do not follow neat jurisdictional outlines. Ethics require good pain management; fear of legal sanctions restricts it. Ethics reach high; law is the lowest common denominator of behavior. For some practitioners, legal concerns have acquired unsupported mythic qualities that may stand in the way of ethical practice. This chapter will dispel some of the more common myths and highlight emerging tort issues that will bring legal pressure on risk managers to emphasize palliative care.

The chapter (a) gives the reader an overview of the important areas where law and palliative care intersect, (b) demonstrates that the law does not hinder good palliative care, and (c) highlights the importance of knowing your own state's legal requirements. It will review the facts underlining fears that treating pain leads to regulatory or criminal sanctions. Although those do happen, this chapter's message is that a practitioner who pays attention to good communication, is familiar with the clinical standards of practice, and documents his or her decisions can safely conform to the ethical obligation to provide palliative care.

INFORMED CONSENT

All content in this chapter presumes the patient has given informed consent. Failure to obtain informed consent risks claims of battery and malpractice, discussed below.

State statutes and judicial precedent define informed consent. Generally, they codify good medical practice. A practitioner must provide information on the risks, benefits, and alternatives to a particular course of treatment in sufficient detail that a reasonable person could rely upon it to make an informed decision. Palliative care requires special attention to informed consent because the emotional stakes are high, and the patients may not be at the top of their listening form. There remains a serious ethical debate in the palliative care community about truth telling at end of life (2).

Some, but by no means all, states recognize the ambiguities of informed consent at life's end. For example, they would permit a defense to failure of informed consent on the basis that professional judgment was exercised and informed consent adapted to prevent emotional suffering or loss of hope in a dying patient. Unfortunately, no consistent precedents guide the practitioner in making these judgments. The balance between paternalism and the “deplorable practice of truth dumping” (2) probably argues for sensitive truth telling rather than truth withholding. There is a broad area between “dumping” dire information and obtaining truly informed consent. The practitioner who opts for protecting the patient from grim facts should assure him or herself that it is a mature and careful decision, not a failure of will.

WITHDRAWING AND TERMINATING LIFE-SUSTAINING TREATMENT

When and how to stop aggressive curative care is a vital ethical issue. The ethical question is, however, infused with legal provisions that run from the highest areas of constitutional law to the minutia of state requirements defining who may make the decision to forgo care and when and how the decision is made. The state laws are not complicated and are designed in significant part to *protect* conforming practitioners from liability.

ATTENDING PHYSICIAN DECIDES WHO IS COMPETENT

Only a patient with decisional capacity may give informed consent. The Uniform Health Care Decisions Act (“Uniform Act”) § I (2) defines capacity as “an individual's ability to understand the significant benefits, risks, and alternatives to proposed health care and to make and communicate a healthcare decision” (3). All states give the attending physician the right and the responsibility to determine whether the patient has capacity. This is a legal obligation of the physician and a duty owed to the patient. In practice, ethical and psychiatric consultations can help form the decision, and there is leeway for sensitive discussions with family members. If family members disagree, they must to take their concerns to probate court.

COMPETENT PATIENTS CALL THE SHOTS AFTER BEING INFORMED

Competent adults have an almost unlimited right to refuse medical treatment and to withdraw from treatment. The Tenth Amendment to the U.S. Constitution reserves to the people fundamental rights not otherwise enumerated in the Bill of Rights and protects them against federal encroachment. The Supreme Court has held that one of those “penumbral rights” is an interest in personal privacy on matters of importance such as reproductive rights and health care decisions. The Fourteenth Amendment's “liberty” interest protects the individual against state laws that might encroach on the right to privacy. State constitutions vary in their language, but all offer competent adults the ability to withdraw from or refuse medical care.

Competent patients do not have to be terminally ill to refuse or withdraw treatment. The decision does not have to make sense to the medical team or be in the patient's best interests. The family does not have to agree and, unless the patient is a minor, does not even have a legal right to know. In some jurisdictions, there is a

“mature teen” exception so that some minors can call their own shots.

The practitioner's legal duty is to fully inform the patient, make sure the consequences and risks are understood, and then either respect the patient's instructions or refer the patient to another doctor who will. The last obligation is important. No state requires a practitioner to physically take the acts necessary to withdraw treatment if he or she has an ethical objection. The obligation to refer is clear but the statutory language allows an inference that if there were no other practitioners available, the provider's moral concerns would trump the patient's right.

PATIENT LACKING DECISIONAL CAPACITY MAY ALSO REFUSE LIFE-SUSTAINING TREATMENT

Incompetent patients retain rights to refuse or authorize treatment but the state has considerably more control. The seminal case from the U.S. Supreme Court is *Cruzan v Director, Missouri Department of Health* 497 US 261 (1990). In that case, Nancy Cruzan was in a persistent vegetative state, kept alive by artificial feeding and nutrition. Her parents and doctors advocated removing the feeding tube. The hospital refused. The Supreme Court refused to require the tube's withdrawal. The opinion affirmed the right of incompetents to have expressed treatment decisions honored but also held that the right may be limited by the states to serve legitimate state concerns. These include protection of life, preservation of the medical profession's integrity, prevention of potential abuse by surrogate decision makers, and prevention of suicide (4). In some states, there is also a limited consideration of family circumstances. All such state restrictions will be strictly scrutinized by the courts for legitimacy. Against that framework, the Supreme Court upheld Missouri's requirement that in the absence of written directives, advocates for treatment withdrawal would have to show by “clear and convincing evidence” that the patient would have wanted treatment to be withdrawn. It further found that the evidence presented by the Cruzan family was not sufficient.

Cruzan highlights the need for practitioners to know what the state standards and procedures are. All states allow a competent person to express his or her wishes for treatment if he or she becomes unable to make those decisions. These laws establish various forms in which the decision can be expressed, usually through either an advance directive for health care (“advance directive”) or a health care power of attorney (“power”). If no such document exists, which is the case for over 80% of terminally ill patients, then state law defines who may make the decision for the patient and what standards will be applied.

A practitioner who conforms to the statute will be protected from civil or criminal actions stemming from withdrawal of treatment. Following a hospital protocol that does not reflect state law is not good enough. A nonconforming hospital protocol has no legal effect and does not offer the practitioner legal protection otherwise available under state laws.

ADVANCE DIRECTIVES AND HEALTH CARE POWERS OF ATTORNEY

Until very recently, there was no legal mechanism that a competent person could use to direct what care he or she wanted in the way of medical treatment if he or she lost decision-making capacity. In common law, only a testamentary will, with the formalities of witnesses and signatures, survived a person's incompetency and death. Testamentary wills, however, have no legal effect until after death and therefore cannot be used to effect health care directives. Other common law powers of attorney were ineffective because they were not “durable.” They lost all effect if the principal lost decision-making capacity.

Advance directives and durable health care powers of attorney were created by statute to bridge this decisional gap between legal competency and death. The two instruments have similar purposes and legal significance but different limits. Advance directives (living wills) record the wishes of competent patients for their care—and most specifically their desire to refuse care—if they become terminally ill or permanently unconscious. The advance directive is essentially self-executing once the qualifying criteria are met. It binds the health care providers once they become aware of it—and they must inquire. A federal statute, the Patient Self-Determination Act (5), requires hospitals and nursing homes to advise patients on admission of their right to accept or refuse medical care and to execute an advance directive. Compliance with the act is a condition for Medicare and Medicaid reimbursement. Very few patients take advantage of the advice although studies show that the compliance rate increases when physicians encourage their patients to create an advance directive (6).

A health care power of attorney achieves the same effect, but operates differently. It delegates the patient's own decision-making right to someone else as of the time that the patient becomes incompetent. It is not self-effectuating: the agent has to act. A well-drafted power will include instructions to guide the agent's decisions, but is not required to do so. Moreover, unlike advance directives, a patient need not be terminally ill or permanently unconscious for the power to be exercised, although the surrogate's options in some states may be limited if the patient is not terminally ill or if the power is not sufficiently specific. The most common limitation is on the agent's power to demand withdrawal of artificial feeding and hydration.

Generally Applicable Requirements for Advance Directives and Health Care Powers of Attorney Formalities

Because they may hasten the death of a then-helpless person and are conceptually extensions of the testamentary will, *written* directives or powers of attorney must be formally executed. They are invalid if they do not meet the prescribed formalities. Most commonly, two adults must witness the documents. Their signatures attest that the patient was “of sound mind” at the time of execution. Statutes generally provide that the agent may not be a witness. They also prohibit the patient's health care providers or their employees from being witnesses and they also may not be the appointed agent. Concerns about conflict of interest or coercion are otherwise too strong. Exceptions in some states permit practitioners to be agents for patients who are close family members.

Effective Only on Incompetence

Although patients must be competent to make directives or appoint agents, their directive becomes effective *only* when they lose decisional capacity as determined by the attending physician. In addition, advance directives are only effective if the patient is terminally ill or permanently unconscious. (States vary in the precise formulation.)

Validity in Other States

There is a widespread but outdated belief that directives or powers executed in one state will not be honored elsewhere. In fact, such documents are statutorily presumed valid in other states and the practitioner may rely on them unless actually informed that the document is invalid. The only exception to the rule of presumptive validity is when an out-of-state power or directive requires some action that is illegal in the practitioner's state. In those circumstances, state law limits the practitioner although the instrument remains valid and effective to direct decisions that are legal in the practitioner's state.

May Be Orally Made or Revoked

Contrary to common belief, most states allow a power of attorney or advance directive also to be made orally by a competent patient. Rules vary about how oral statement must be witnessed and recorded in the patient's chart. In addition, most states allow a patient to *revoke* a written or oral directive or power of attorney orally. An oral revocation must be documented in the patient's chart and is not binding on the practitioner until that happens. Many states impose penalties if a person who hears an oral revocation fails to bring it promptly to the attention of the attending physician. Some states provide that an oral revocation must be made directly to a health care provider. Many states make it a criminal offense to conceal or destroy a power or directive.

Most state laws do not specify that the patient must be competent to effect revocation. A number of states actually specify that the patient does *not* have to be competent to revoke an advance directive or appointment of a surrogate. Nonetheless, oral revocation by an incompetent patient is problematic particularly if the family is not united. There are not enough precedents to generalize about liability risks when an oral revocation is challenged. Prudence dictates that the revocation be well documented by identifying the person who heard the statement, additional witnesses if any, and the date, time, and context of the statement. The witness statement should be written and confirm the substance of the statement. The practitioner should be cautious to make sure that the state's formulation is followed. For example, if only health care practitioners can witness an oral revocation, respecting a family member's statement alone would not be appropriate.

Emergency Exceptions

Emergency room personnel do not have to spend time searching for an advance directive (7). However, they must honor an advanced directive or do not resuscitate (DNR) order that is brought to their attention. In most states, wearing an approved DNR bracelet is recognized by law as a way to notify emergency providers that a DNR is in effect.

Emergency medical technicians have traditionally been unable to honor an advance directive even if it is presented to them. Recently, however, many states have initiated programs under which emergency medical technicians may honor DNR or other orders if the patient is identified, usually by a bracelet, as having an active order or directive.

WHO ACTS FOR THE PATIENT?

Advance Directive

A valid advance directive trumps all other notions about what care should be offered if the patient's condition reaches the stated criteria. If an advance directive is coupled with a health care power of attorney, the agent is bound by the directive (8).

Health Care Power of Attorney Unaccompanied by Directives

A validly appointed health care proxy has virtually the same authority to act as the patient would have if competent. An exception in some states prevents proxies from authorizing withdrawal of artificial feeding and hydration unless the patient is terminally ill or permanently unconscious or has expressly provided consent in an advance directive or in the document appointing the agent. Missouri does not allow a proxy to withdraw feeding or hydration at all (10). This restriction and, in fact, the more common restriction on removal of feeding and nutrition where the patient did not specifically authorize its withdrawal in an advance directive or power of attorney, may violate both the federal and state constitutions. Courts have consistently held that artificial feeding and hydration are forms of medical treatment. They have not indicated that there is a justifiable difference between forgoing other life-sustaining treatments and forgoing or withdrawing artificial feeding and nutrition and at least one state has held such a limitation unconstitutional (11). Courts have also held that federal statutes requiring nursing homes to provide feeding and hydration do not limit the right to refuse or withdraw from treatment (12).

When the Patient Has No Directive or Appointed Health Care Agent: Surrogacy

Although much is written about advance directives and health care proxies, most adult patients have neither. When the physician decides that his or her patient lacks capacity, state law identifies a person, or class of persons, to act as decisional surrogate. In most states, there is an order of surrogacy or surrogacy classes: the spouse (legally separated and exspouses excepted), an adult child, and then to an adult sibling. Some states continue the list of classes to more remote relatives—grandchildren, cousins, and the like. Increasingly, states are recognizing that patients' families can be fragmented, scattered, or simply unknown. These states add a category of persons who have “exhibited special care and concern for the patient, who is familiar with the patient's personal values, and who is reasonably available” (13). A very few states give domestic partners the same status as spouses. Colorado permits the entire group of relatives and those friends with a good idea of the patient's wishes to reach a consensus as to who the surrogate should be (14). In all states, if no surrogate of any level is available, a guardian appointed by the probate court must authorize withdrawal of treatment for the incompetent patient.

Almost all states also have some form of “surrogate tie breaker.” If the members of a surrogacy class, such as adult children, cannot agree, state laws usually require the practitioner to honor the wishes of the majority. If the majority deadlocks, the decision may have to be referred to a court or to the next lower priority group.

In every state, the surrogate is obligated to follow the patient's wishes to the extent those are known. If they are not known, every state requires the surrogate to act in good faith and in the “best interest” of the patient. Most states have procedures by which a surrogate not acting in the patient's best interests can be removed or instructed by a court. In those cases, the challenger has the burden of proof and will have to show by “clear and convincing” evidence (a high standard of proof) that he or she knows better what the patient would have wanted. Some states provide that a health care provider has standing to bring an action to have an agent removed. In others, that is less clear.

Statutes Absolve Practitioners Who Act on Best Information

A major purpose of surrogacy laws is to clear the practitioner's way and protect him from liability if he relies on apparently valid instructions from the patient or a surrogate. Statutes generally permit any practitioner to rely on a properly executed written or oral advance directive or health care proxy until informed that it is not valid. The statutes do not require the practitioner to resolve the issue of validity—that is for the courts. Similarly, the practitioner must make “reasonable efforts” to identify potential surrogates, but that does not entail a broad search. The practitioner must ask present or known and reachable kin and friends about other potential members of surrogate classes. A few statutes provide that the practitioner can rely on the notified kin and friends to locate and tell others.

The protection is broad. A practitioner who reasonably relies on a directive or surrogate's instructions is exculpated from both civil and criminal liability if the instructions cause or hasten death. There has *never* been a successful case against a doctor for withholding or withdrawing treatment under the post-*Cruza,*, advance decision-making statutes.

TREATING PAIN: HASTENING DEATH?

Americans fear unrelenting pain as death nears far more than they confess to fearing death itself. Studies also show that despite significant advances, the fear is entirely reasonable. Undertreated and untreated terminal pain remains exceedingly common as are treatable symptoms such as anxiety, depression, and dyspnea.

Undertreatment continues although palliative care experts urge that 95% of terminal pain can be treated. (With terminal sedation, there is no reason why that figure would not be 100% if the patient or surrogate so chose.) It persists despite significant literature on the physiology and methods of pain management and the exhortations of leading medical and governmental organizations.

This failure is unethical: “Physicians have an obligation to relieve pain and suffering and to promote the dignity and autonomy of dying patients in their care. This includes providing effective palliative treatment even though it may foreseeably hasten death” (15). Patients near the end of life must continue to receive emotional support, comfort care, *adequate pain contro*l, respect for patient autonomy, and good communication (16).

Although there is no direct authority, legal hindrances to treating the pain of the dying may violate the U.S. Constitution and may also be illegal under state constitutional theories (17). That suggestion was certainly made in various opinions by Supreme Court justices in the context of finding no federal right to physician-assisted suicide. States have taken legislative action to improve the treatment of pain. California's Pain Patient's Bill of Rights requires physicians to treat pain or refer the patient to a pain management expert. In 2001, California began to require that every health care licensee receive treatment in pain management as a condition to being allowed to renew his or her professional licenses (18). In 2000, Florida required health care providers to treat pain on request (19). In Oregon, failures to treat severe pain caused a physician to incur sanctions and license limitations (20). Other license board complaints by families who watched loved ones die in pain and fear are pending and are becoming increasing more frequent.

Physicians' fears are the leading cause of undertreated pain. A recent survey of nearly 400 physicians found that more than 25% were concerned about their patients becoming addicted to pain medication, and a significant number were afraid of investigation by a drug regulatory agency (21). The same survey found that 30% of physicians would be reluctant to provide opioid therapy to patients with severe and intractable pain, and 10% would provide opioids only to patients with 1 year or less to live. A survey of members of the American Pain Society found that undertreated pain is the major ethical concern of the respondents (22). Yet, where pain is documented and treated within well-known guidelines that are no more than good medical practice, those fears are dramatically overstated.

The number of patients who have experienced excruciating pain because of a practitioner's over-perception of criminal or civil risk is shamefully large. Cases finding criminal or civil liability for medical personnel who document and treat pain intelligently are almost nonexistent. The use of opioids for cancer pain is virtually enshrined in medical board guidelines.

CRIMINAL SANCTIONS FOR HASTENING DEATH: INTENT IS EVERYTHING

Intending to treat pain and ease suffering is palliative care even if it causes or hastens death. Intending to cause death, even with a merciful intent, is not legal anywhere in the United States (23). Physician-assisted suicide is legal only in Oregon (24). Even there it is used infrequently (25). Identical acts, identical results; the *critical* difference is the practitioner's *intent*.

The concept of intent in palliative care scares medical practitioners. “How would they know what I intend?” “We can't have laymen judging what's in a doctor's mind!” Intent, however, is the cornerstone of much of our criminal law. Courts are accustomed to dealing with proof of subjective “intent”; the phrase has significant legal meaning. In general, the intent proven must be intent to accomplish the specific illegal act charged. The state has the burden and it must prove intent “beyond a reasonable doubt.”

Criminal intent can be proven directly (a confession) or indirectly (circumstantially) by inferences reasonably drawn from all the facts and circumstances. However, when intent is proven circumstantially, the evidence *must* be consistent with the inference drawn and *may not* be consistent with *any* innocent intent. This is a very high

hurdle when palliative care is involved. Motive is also a problem for prosecutors. Medical practitioners have nothing to gain by a hastened death. Since 1980, no practitioner has been ultimately found to have the requisite intent for a criminal conviction when the defense claimed that the motive was palliative care. Dr. Kevorkian's case is no exception because he admitted an intent to cause death (26). Several cases illustrate the respect that courts have developed for aggressive palliative care.

State v Naramore

In 1996, a Kansas jury convicted Dr. Stanley Naramore of attempting the murder of an elderly cancer patient (27). Her family asked for better pain control. Dr. Naramore detailed the risks and administered a first dose of morphine. Her family interpreted a later ambiguous remark to mean that he actually intended to hasten her death. There was conflicting evidence as to whether Dr. Naramore had injected or prepared to inject the patient with Naloxone, which the prosecution took as an admission that he had consciously "gone too far."

Dr. Naramore was also charged with murder after a diabetic patient with heart disease refused blood thinners and suffered a serious stroke. After extensive efforts, Dr. Naramore and a second doctor determined that the man was "brain dead." He was extubated and died. The prosecution claimed that the patient was actually legally alive at the time but paralyzed by a drug. They claimed that extubation caused his death.

Dr. Naramore flatly denied any intent to cause death in either case. The state's proof of intent was entirely circumstantial. Its experts' testimony that Dr. Naramore's actions were outside the standard of care, and therefore presumably not intended to palliate, was rebutted by equally credentialed defense experts.

The Kansas Supreme Court summarily reversed both convictions. Its reasoning is important to any practitioner and accordingly is quoted below at some length. It held that the trial court erroneously failed to instruct the jury on the ambiguities and difficulties of palliative care. More important, it held that no reasonable jury could have found guilt "beyond a reasonable doubt" when medical experts so substantially disagreed.

> When there is such strong evidence supporting a reasonable, noncriminal explanation for the doctor's actions, it cannot be said that there is no reasonable doubt of criminal guilt. This is particularly true … where the only way the defendant's actions may be found to be criminal is through expert testimony, and that testimony is strongly controverted in every detail.
>
> We do not say that a physician can always escape criminal conviction for reckless or purposeful homicidal behavior through friendly medical testimony on his or her behalf. *But there is a reason why there has yet to be in Anglo-American law an affirmed conviction of a physician for homicide arising out of medical treatment based on such highly controverted expert evidence as here.*
>
> All three amicus briefs acknowledge the appropriateness of criminal responsibility where a practitioner's actions are clearly reckless or purposefully homicidal. However, they note that if criminal responsibility can be assessed based solely on the opinions of a portion of the medical community which are strongly challenged by an opposing and authoritative medical consensus, we have criminalized malpractice and even the possibility of malpractice.
>
> The instant case is a very good example of this. With no direct evidence of criminal intent, it is highly disturbing that testimony by such an impressive array of apparently objective medical experts, who found the defendant's actions to be not only noncriminal, but medically appropriate, can be dismissed as "unbelievable" and not even capable of generating reasonable doubt.
>
> —*State v Naramor*e, 965 P2d 211, 223–24 (Ks 1998)

United States v Wood

The reasoning in *Naramore* was subsequently applied to reverse the involuntary manslaughter conviction of a Veterans Administration doctor. The doctor injected a patient he believed to be "drowning in his own fluids" with potassium chloride. Two nurses refused to give the injection and warned the doctor that the rate of injection exceeded hospital policy. All agreed that some amount of the drug was appropriate.

The Court concluded that a rational jury could not infer from the evidence that the doctor acted with malice (intent) or in a manner that was wanton, reckless, or in gross disregard for accepted standards of care (28). The court reasoned that "[the doctor's actions] involved a choice between several courses of action, some of which were more risky, but perhaps more efficacious than others. *A physician cannot be convicted of murder simply for adopting, in an emergency setting, a risky course of action intended to prolong life that, when carried out fails to forestall or even hastens death*." (202 F3d. 1222 [10th Cir. 2000] at 1232)

The reversals of *Naramore* and *Wood* stand for the proposition that intent cannot be inferred circumstantially where credible medical experts disagree. Even involuntary manslaughter, which does not require malicious intent, requires evidence of care that is so substandard recklessly low that it denotes indifference to human life. This standard is far more demanding than the proof required to demonstrate medical malpractice.

TERMINAL SEDATION IS NOT CRIMINALIZED

Supreme Court Carefully Distinguished between Assisted Suicide and Terminal Sedation

The law recognizes terminal sedation as a palliative approach even when death might be hastened or caused by the sedating medication. Terminal sedation is distinguished from murder, euthanasia, and assisted suicide. All states that explicitly criminalize physician-assisted suicide carve out palliative care when there is no intent to cause death, even when the care might hasten the death (29).

The Supreme Court's assisted suicide cases explicitly distinguished between terminal sedation and assisted suicide on the basis of the practitioner's intent. Writing for the majority in one of the cases (30), Chief Justice Rehnquist conceded that the line might be fine, but affirmed the states' freedom to draw it.

> Just as a State may prohibit assisting suicide while permitting patients to refuse unwanted lifesaving treatment, it may permit palliative care related to that refusal, which may have the foreseen but unintended "double effect" of hastening the patient's death.
>
> —521 US 793, 808 n.11

(No federal or state court has since addressed terminal sedation in any context.)

Do patients have a legal right to receive palliative care up to and including terminal sedation? Justice O'Connor's concurring opinion in *Quill* suggests at least that states may not be free to infringe on access to palliative care.

> The parties and *amici* agree that … a patient who is suffering from a terminal illness and who is experiencing great pain has no legal barriers to obtaining medication, from qualified practitioners, to alleviate that suffering, even to the point of causing unconsciousness and hastening death.… In this light, … I agree that the State's interests in protecting those who are not truly competent or facing imminent death, or those whose decisions to hasten death would not truly be voluntary, are sufficiently weighty to justify a prohibition against physicianassisted suicide.
>
> —521 U.S., at 736–736, internal citations omitted

Justice Souter added:

> I do not believe … that this Court need or now should decide whether or not a … [a right to assisted suicide] is "fundamental." That is because, in my view, the avoidance of severe physical pain (connected with death) would have to constitute an essential part of any successful claim and because, as Justice O'CONNOR points out, the laws before us do not force a dying person to undergo that kind of pain. [They] … do not prohibit doctors from providing patients with drugs sufficient to control pain despite the risk that those drugs themselves will kill.
>
> —Id. at 785, internal citations omitted

These justices thereby uncoupled the state's right to forbid physician-assisted suicide from a right of patients to have their pain controlled even if death is thereby

facilitated.

In sum, the practitioner who intends to treat pain and does so with a decent respect for the standards of care has no reason to fear legal sanctions in the palliative context. A wise practitioner dealing with a seriously ill patient will assess and document pain and treat it aggressively. Except under Oregon's procedures, a physician who is asked to help a patient die by providing or administering a lethal dose of any medication *must* decline. However, ethically the physician *must* also make and keep a promise that pain and other symptoms will be treated even up to the point of sedation if that is what the patient or surrogate wants. If the physician cannot keep that promise, referral or consultation are not only appropriate but also required.

Physician-Assisted Suicide Is Presently Legal Only in Oregon

In all states but Oregon (31), assisted suicide is either specifically illegal (32) or presumptively illegal (33). In states where there is no statute at all, the act is regarded as illegal and punishable as a “common law felony.” [These deeds were felonies at the time the state constitutions were created but were never formally reenacted by statute. These “saved crimes” are now lumped together as minor felonies (34).] Relying on the “saved crimes” concept, the Michigan Supreme Court held that Dr. Kevorkian could be indicted for assisting a suicide even though the state had no assisted suicide statute on the books. Physician-assisted suicide is also a specific violation of federal law when conducted on a federal property, and federal funds may not be used in any jurisdiction to support physician-assisted suicide (35).

The Oregon statute is quite limited. The patient must be legally competent, a legal resident of the state, and have a life expectancy of 6 months or less. The patient must make an initial request both orally and in writing. An attending and a consulting physician must independently certify to the diagnosis and prognosis and that the patient is competent, not depressed, and has been informed of available options such as hospice, comfort care, and pain management. After certification the patient must again request assistance orally and in writing and then must repeat the request orally after a 15-day waiting period. The patient must also be physically able to take the medication without help. If all these conditions are met, the participating physicians are exempt from any penalties relating to suicide or murder and the patient's death does not constitute suicide for insurance purposes (36). Oregon's statute remains controversial. There have been several efforts to pass federal legislation that will preclude the use of federally controlled substances in assisted suicide. In 2001, the U.S. Attorney General instructed the DEA the department would not consider assisted suicide as a “legitimate medical purpose” under the Controlled Substances Act even if state law permitted the practice. Oregon promptly sued and a federal court enjoined implementation of the Attorney General's interpretation.

PALLIATING CHRONIC INTRACTABLE PAIN REQUIRES CLOSE ADHERENCE TO GUIDELINES

Untreated, chronic, intractable pain is epidemic in the United States and worldwide. The failure to treat it in the United States is directly a product of the fear of criminal and license sanctions. This should not be. The ethics of treating chronic pain are the same as for terminal pain. All but five U.S. jurisdictions (37) currently have state medical board guidelines and/or statutes that explicitly encourage treatment of chronic pain with opioids when other analgesic methods are not effective. The statutes and guidelines also set out standards for practitioners. There is no indication that the remaining five jurisdictions are more stringent.

If the state guidelines are followed, the guidelines assure the practitioner that there will be no licensing sanctions. If the state has passed an Intractable Pain Act, the practitioner is also protected from prosecution when guidelines are followed. These guidelines, as represented by the model guideline of the Federation of State Medical Boards, have the informal approval of the U.S. Drug Enforcement Administration.

A physician who prescribes opioids should strictly follow his or her state guidelines, which, in any case, make good medical sense in terms of history, examination, documentation, plan of care, and supervision. Maintaining a patient on opioid therapy without evidence that the patient is functionally better off with the medication than he or she is without, or in disregard of evidence of dysfunction or diversion, should be strictly avoided. Doctors who are subjected to medical board sanctions or investigated criminally almost always have failed to document their examinations, treatments, progress, and plan of care or have been indifferent to evidence of diversion or abuse.

PRACTITIONER LIABILITY FOR INADEQUATE PALLIATIVE CARE

Practitioners need to realize (and communicate to their risk managers) that *undertreatment* of pain is becoming legally risky. It will become more so as the public is educated by palliative care advocates to understand that most pain can be treated. Inadequate palliative care can be malpractice. It can invoke liability for battery, elder abuse, and infliction of severe emotional distress. Patient advocates are pushing hard to focus state medical boards, accreditation organizations, and the “fraud and abuse” investigators of Medicare/Medicaid bureaucracies on inadequate palliative care.

RISK OF MALPRACTICE LIABILITY IS SUBSTANTIALLY INCREASED BY NEW GUIDELINES AND STANDARDS FOR PAIN ASSESSMENT AND MANAGEMENT

Medical malpractice is a specialized branch of negligence law. To show malpractice, a plaintiff must prove by a preponderance of the evidence: (a) a legal duty of care, (b) a breach of the duty by the defendant, and (c) damages that are proximately caused by the breach. Each of the required elements has an accretion of law.

Duty of Care

As relevant here, duty is established by proof of a doctor (nurse)/patient relationship or a hospital/patient relationship. It is a given in cases that involve failure of care in most institutional settings.

Breach of Duty

A practitioner breaches the duty of care by falling short of the standard of care “in the community” for whatever treatment or decision is at issue. Both the existence of the standard of care and failure to meet the standard *must* be shown through expert medical testimony. If the practitioner is a specialist, the testimony must show that he fell short of the standard of care for the specialty, which might be higher than the standard applicable to a general practitioner. The jury must believe that the care fell culpably short of what a hypothetical “reasonable practitioner” faced with the same patient in the same condition would have been expected to provide. The standard of care never requires perfection. Finally, the plaintiff has to show that the practitioner's negligent acts proximately caused a cognizable injury.

The critical hurdle for malpractice actions based on inadequate control of pain and other symptoms of the terminally ill has been the “standard of care.” A practitioner cannot breach a standard of care until one exists. Until very recently, there was no medical consensus on clinical management of pain, or even agreement that a practitioner had a responsibility to relieve pain and suffering. Physicians were not well educated in pain management, and there were few resources available. “Not very good” *was* the “standard of care.”

That has changed (38). A consensus on good pain management practice has been building strongly for 10 years and has existed at least since the mid-1990s in a form sufficiently official to be useful in litigation. The pain management standards made applicable to every facility accredited by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) are clear evidence that there is a standard for pain assessment and treatment (39). JCAHO hardly stands alone. The American Medical Association's program for Education for Physicians on End-of-life Care provides concise information on pain management with many references. It is being made available to every American Medical Association member. Similarly, a consensus has developed on chronic pain management that encourages use of opioids as a legitimate part of pain management. The Federation of State Medical Boards, after long study, published model guidelines for physicians treating chronic pain with opioids. They have been adopted as law or guidelines in 38 states (40).

Injury and Damages

The final ingredient in a malpractice case is proof of injury and entitlement to damages for that injury. This remains a difficult burden because it requires a different analysis than other medical injuries. In the classic malpractice case, harm is done by a practitioner's inept treatment or failure to be aware of what treatment is called for. Therefore, pain and suffering related to that failure is a separate cognizable component of the damage (41), not the injury itself. Pain alone, without a physical manifestation, was not considered an injury. Not providing pain medication does not increase costs. If a patient died, it was due to the underlying disease, not the treatment or lack of it. Pain was just part of the overall sad circumstance.

This analysis is no longer justified. The fact that pain can be treated separately from the disease and even can be treated when the disease is beyond treatment changes the analysis. It is also clear that untreated pain itself can cause more pain and do long-term physical and emotional damage (42).

In 1993, a North Carolina jury found a nursing home liable for pain and suffering experienced when a nurse, concerned about “addiction,” substituted weak analgesics

and a mild antidepressant for morphine ordered by the physician to treat the pain of end-stage prostate cancer (43). After extended testimony on the duty to treat pain and the standard of care for pain management, the jury awarded $15 million in compensatory and punitive damages. In approving a later settlement, the trial judge noted that the claim was for pain and suffering alone, not for wrongful death or some other harm to the patient (43).

Shortly thereafter, the Sixth Circuit affirmed a “pain only” injury under Tennessee law. The plaintiff and her husband were admitted to a hospital following a car accident. They were officially discharged (for transfer to another hospital as arranged for by the defendant) at midmorning. Due to transportation delays, they did not leave the hospital until the next evening. While they waited, hospital staff refused to give any pain medication, and medical records did not reflect visits from the doctor. As part of a larger judgment, plaintiff was awarded $25,000 in compensatory and punitive damages for the pain and suffering the plaintiff claimed had resulted from the doctor's abandonment and negligence (44).

INADEQUATE PAIN MANAGEMENT MAY CONSTITUTE “INFLICTION OF SEVERE EMOTIONAL DISTRESS”

The law recognizes two different kinds of infliction of emotional distress—negligent and intentional. Either of these could apply to a patient or to the family of a patient who has been subject to inadequate pain treatment.

A successful plaintiff in an emotional distress case is entitled to damages for mental distress or emotional disturbance that result from either purposeful or willful conduct by the defendant (intentional infliction) or indifferent and negligent behavior (negligent infliction). The difference is a matter of degree. Both require actions that cause actual consequences for the victim's physical or emotional health (45). Most states require that the plaintiff show that the emotional distress suffered had physical consequences such as sleep disruption, headaches, or gastrointestinal problems (46). However, 14 states allow recovery for emotional distress without requiring any physical manifestation (47).

Intentional infliction, a more serious complaint, has four elements. The defendant must act intentionally or recklessly, the conduct must be extreme or outrageous, the conduct must be the cause of the emotional distress, and the distress must be severe (48). The outrageousness of the defendant's conduct can be proven by the plaintiff's testimony. The severity of the distress must usually be proven by expert testimony. A physician, for example, might testify to treatment of the plaintiff for insomnia, nightmares, anxiety, or depression. Courts have held that “[p]hysical manifestation of emotional distress … may serve as proof of serious mental injury. Moreover, evidence that a plaintiff has suffered from nightmares, insomnia, and depression or has sought psychiatric treatment may support a claim of serious mental injury” (49). It also appears that next of kin of terminally ill patients are almost by definition in a precarious emotional state so that they are more easily distressed by callousness or negligence (50).

Emotional distress has a long-standing application in medical lawsuits. A physician can be held liable for mental and emotional anguish suffered by a patient due to negligent care or reckless misconduct. Some jurisdictions also employ a bystander rule that allows family members to recover for the emotional distress caused by watching a relative suffer negligent medical treatment. For example, parents have been allowed to sue for the negligent treatment of a newborn infant who was presumed dead by the hospital staff but turned out to be alive (51), for the negligent mishandling of a deceased child's body (52), and for observing the death of a newborn child due to alleged negligence by the obstetrician and staff (53). The same approach should also apply to those who watch loved family members suffer due to failure to treat pain. The analogy to the labor and delivery cases is clear in the hospital or nursing home setting where the patient is obviously suffering. The doctrine is “arguably applicable to any instances of intractable pain and its poor management in extreme cases” (54).

INADEQUATE PAIN MANAGEMENT MAY BE ABANDONMENT OF THE PATIENT

When a doctor agrees to treat a patient, that doctor has a duty to give the patient all necessary attention for as long as the patient needs it (55). A physician who leaves a patient at a critical stage of treatment without giving the patient adequate notice and time to choose another caregiver has abandoned the patient (56). Abandonment of a patient by his or her physician is a tort (57), and a physician who does it is liable for damages.

To prove abandonment the patient must show four things: Abandonment cannot take place without an established physician-patient relationship (58). The physician must have terminated his or her relationship with the patient or neglected the patient. The termination must have been done without reason or without sufficient notice to allow the patient to choose another physician, and the patient must have been injured as a result (64).

A physician who promises to help manage a patient's pain and then fails to do so may be found to have abandoned the patient. In one case (60), the patient's obstetrician promised to provide anesthesia for the patient's labor and delivery. The patient went into labor while the physician was away on a fishing trip, and the substitute obstetrician refused to give her any anesthetic. The patient sued for abandonment, arguing that she had not been given adequate notice or time to choose her own substitute obstetrician and that she had been injured by being deprived of the promised anesthesia. The court found that so long as the patient had not been given adequate notice, she had been abandoned, and the lack of help managing her pain during delivery was an injury. *Lynch v Bryant*, discussed above (see the section Injury and Damages) in the context of severe emotional distress, is also an abandonment case.

TREATMENT IN EXCESS OF PATIENT DIRECTIVES CONSTITUTES MEDICAL BATTERY

Medical battery occurs when the medical treatment given to a patient exceeds the patient's consent (61). It requires proof of an unwanted touching (medical care) but does not require physical harm and, in fact, the touching can be relatively trivial or even arguably beneficial. It is well established that failure to honor DNR orders or advance directives constitutes battery. In *Leach v Shapiro* (62), for example, an Ohio Court of Appeals found that there had been harmful contact when a woman in a chronic vegetative state was placed on life support without her consent. Similarly, a Michigan jury awarded surviving family members approximately $16 million for mental anguish and past and future expenses for medical care after life-sustaining procedures were performed in direct violation of a surrogate's instructions pursuant to a durable power of attorney for health care. A limited number of state statutes go further to create a specific cause of action when a practitioner fails to honor an advance directive or a living will (63).

TREATMENT IN EXCESS OF PATIENT DIRECTIVES MAY NOT BE “MEDICALLY NECESSARY” FOR PAYMENT PURPOSES

When a health care provider submits a request for insurance or Medicare/Medicaid reimbursement, he or she certifies that the service was reasonable and necessary (64). The federal program is required by law to deny payment for inappropriate services (65).

The legislative history of Medicare/Medicaid shows the importance Congress placed on a physician's certification that the care given is necessary. “The physician is to be the key figure in determining utilization of health services…. It is a physician who is to decide upon admission to a hospital, order tests, drugs and treatments, and determine the length of stay. For this reason the [Medicare statute] would require that payment could be made only if a physician certifies to the medical necessity of the services furnished” (66).

There are several ways that the certification's validity could be questioned in terminal care. If an advance directive precludes resuscitation, charges for life-prolonging resuscitation may not be necessary. Similarly, there is a reasonable argument to be made that any aggressive curative care to a patient who is terminally ill is legally unnecessary unless the patient is also advised that hospice care is an available alternative form of treatment. Although hospice issues are outside the scope of this article, a physician's failure to fully explain the hospice alternative to Medicare and Medicaid beneficiaries is a severe detriment to quality of life in terminally ill patients who might choose to take advantage of it if properly informed.

ELDER ABUSE STATUTES AND FAILURES OF PAIN MANAGEMENT

Older Americans are disproportionately represented in the sick and dying. Older Americans who are sick and dying receive less medication for pain than younger people (67), and demented older people receive less pain management than their competent contemporaries (68).

Almost every state has some form of elder abuse or adult protective services statute that defines elder abuse and provides a remedy for abusive actions. Most of the statutes protect disabled adults of any age. Combining these facts with the JCAHO pain standards applicable to hospitals and nursing homes and the American Geriatric Society's guidelines for the management of chronic pain (69), health care providers should be alert to the potential that failure to manage an elderly or incapacitated person's pain will be labeled elder abuse.

In June 2000, a California jury awarded $1.5 million to the family of an elderly man with a metastasized lung and bone cancer (70). He was prescribed low levels of pain medicine while he was in the hospital. Hospital records showed that throughout the hospitalization his pain was rated between 7–10 on an assessment scale. On discharge, although his pain was still rated a 10, he was prescribed oral acetaminophen/hydrocodone, which he could not swallow, supplemented later with a low dose of transdermal fentanyl and a meperidine injection. His doctor flatly refused to prescribe anything stronger despite his continuous pain. After several days, another

doctor prescribed higher doses of morphine, which brought immediate relief.

The physician defended his actions on grounds that he was not sure of the diagnosis as of the time of discharge and feared respiratory depression if morphine were administered. At trial medical experts testified on both sides. However, unlike criminal statutes, civil cases do not have to be proven “beyond a reasonable doubt.” Rather, they are judged on a much less stringent “preponderance of the evidence,” and the jury was free to weigh the expert testimony and find for the plaintiff.

This case is significant because it directly addresses pain and because the California elder abuse statute (71) requires proof (by a preponderance of the evidence) of reckless and malicious behavior to find liability. Many states have a lower standard in their elder abuse statutes and appear to require less stringent evidence of neglect or pain. They impose liability without the heightened “malicious and reckless” standard used in California. In addition, elder abuse statutes often permit punitive as well as compensatory damages and provide that the cause of action will survive the abused adult rather than terminate at his or her death (72). It is reasonable to expect that this cause of action will become far more common in the near future.

CONCLUSION

Both law and ethics require health care providers to walk a middle ground, treating pain and other symptoms aggressively to ease the process of any serious illness but to be wary of prescribing practices that might increase dependence and diversion in predisposed patients. Although some physicians have, understandably, characterized this middle ground as “between a rock and a hard place,” it is far more realistic to think of palliative care as good medicine: you want to deliver it, not deny it. No legal or ethical barriers exist that will hinder a good practitioner from providing palliative care. “Physicians should base treatment decisions on the scientific and medical evidence that is available from many sources. It is time for physicians, nurses, pharmacists, other health care professionals, system administrators, and regulators to come together to ensure improved function and good quality of life for all persons in pain” (73).

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33. In Alabama, Ohio, West Virginia, and Wyoming, assisted suicide is not included in the criminal code but its illegality is implied by references in the state's advance directives statutes that “nothing in this provision shall permit homicide, euthanasia or assisted suicide.”
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67

HEMATOLOGIC SUPPORT OF THE CANCER PATIENT

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Cytopenias are a frequent and sometimes dangerous complication of malignancy and its treatment. The mechanisms causing these are numerous and are sometimes difficult to determine in an individual patient. Originally only armed with transfusion products and time, oncologists now have additional tools to deal with cytopenia. However, the appropriate use of transfusions and growth factors requires both an understanding of the literature and much clinical discretion.

ANEMIA

Etiology

Anemia is a frequent finding and a major factor in morbidity in many oncology patients. More than half of all cancer patients will be anemic regardless of treatment received, and approximately 20% of all patients undergoing chemotherapy will require red blood cell (RBC) transfusion during their treatment course. Patients with lung cancer, lymphoma, genitourinary tumors, and gynecological malignancies have the highest transfusion rates, perhaps due to the higher frequency of myelotoxic therapy to treat these tumors. Anemia within the hematologic malignancies is almost universal.

The etiology of anemia in cancer patients is usually multifactorial and is frequently a complication of both the cancer itself and its treatment. Tumor cells can invade the bone marrow, as in breast and prostate cancer, or can suppress marrow and erythropoietin production by cytokine production. Tumor necrosis factor has been shown to decrease marrow responsiveness, whereas beta interferon is thought to inhibit erythropoietin production within the kidney. Anemia of chronic disease, blood loss, shortened red cell survival, nutritional deficits, and underlying infection (again causing cytokine-related suppression) can be sources of anemia. Less common are acute hemorrhage from the malignancy itself and hemolytic states such as disseminated intravascular coagulation associated with promyelocytic leukemia and sepsis, immune hemolytic anemias from chronic lymphocytic leukemia, and medication-induced hemolysis. Anemia of chronic disease is the most frequent cause and is characterized by normocytic and normochromic morphology on peripheral and bone marrow exam, low serum iron and iron binding capacity, normal or increased marrow iron stores, and blunted erythropoietin levels and response. Finally, the continued bombardment of the marrow by myelotoxic regimens, including the newer combination regimens, can cause significant and prolonged anemia with repeated cycles causing a cumulative injury to production.

Chemotherapy can cause both transient and sustained cytopenia. The storage compartment of the marrow contains enough maturing cells to maintain peripheral counts for approximately 8–10 days after stem cell production ceases. Thus, the effect of cell cycle–specific chemotherapy will be notable by the tenth day after treatment, nadir counts are manifest between days 14 and 18, and recovery occurs between days 21 and 28. In contrast, G_0 active agents are characterized by delayed nadir counts (4 weeks) and prolonged recovery time (6 weeks) owing to the preferential effect on resting stem cells. Repeated dosing of chemotherapy, especially during early marrow recovery, may result in sustained toxicity and persistent pancytopenia. This effect is perhaps most notable with the alkylating agents owing to cumulative DNA damage. Likewise, radiation therapy further contributes to the anemia, particularly when the marrow is already suppressed.

Role of Erythropoietin

Erythropoietin plays a key role in RBC production and in the anemia due to cancer. An obligatory growth factor and regulatory molecule, erythropoietin affects RBC production by stimulating the burst forming units–erythroid (BFU-E) and the colony forming units–erythroid (CFU-E). The BFU-E cells are early cells within erythropoiesis, which proliferate rapidly and have a low number of erythropoietin receptors. Therefore, a higher level of erythropoietin is necessary to stimulate entry into the cell cycle for BFU-E cells. The later CFU-E cells have a high number of erythropoietin receptors and require a constitutive level of erythropoietin for continued survival, growth, and production. Erythropoietin thus shows a keen regulatory mechanism for red cell production. In the adult, approximately 90% of erythropoietin is produced within the peritubular fibroblastoid cells of the inner cortex of the kidney, and the remainder are produced in the liver. Within the peritubular intersitial cells, erythropoietin production is constitutive and inducible, with baseline levels produced from each cell and additional cells recruited to increase production for hypoxic states. As arterial PO_2 levels decrease and tissue hypoxia increases, erythropoietin levels increase, acting as a key regulatory mechanism. Thus erythropoietin has been shown to be responsive to hypoxic states, and as seen in the setting of decreased hemoglobin levels, it increases committed red cell progenitors and the rate of maturation of the reticulocytes. The erythropoietin level is fairly constant for an individual with stable hemoglobin level. It does not vary with gender or age, and has no biologically inactive precursor or stores.

Cancer can affect erythropoietin by decreasing the marrow responsiveness to erythropoietin or by decreasing erythropoietin production, as tumor necrosis factor and some nephrotoxic agents can. In both a rat model and in a group of lung cancer patients, cisplatin was shown to cause depressed erythropoietin levels from the expected compared to controls with similar levels of anemia (1). These patients did not mount the usual increased erythropoietin response levels to anemia after receiving cisplatin but were capable of producing increased levels once cisplatin treatment had been completed and renal function improved. Although this study suggests that patients are unable to support sufficient erythropoietin production, others show that cancer patients are unable to respond to the physiologically increased levels in response to cancer. In a study of 35 patients with lung cancer before initiation of treatment, Dowlati et al. showed that even when anemic cancer patients have increased production of erythropoietin, they have lower ratios of erythropoietin to serum soluble transferring receptors. This ratio is a marker of erythropoiesis and is elevated with increased production. This lower ratio shows that the marrow is not appropriately responsive to the stimulation by erythropoietin (2).

Usually, a decrease in oxygen-carrying capacity results in elevated erythropoietin levels. In fact, Finch (3) found erythropoietin levels increased as hemoglobin levels

dropped below 12 g/dl. However, cancer patients are often resistant to or incapable of producing increased levels of erythropoietin. In a study of 81 solid tumor patients, Miller et al. (4) showed that compared with a group of iron deficient controls matched for hemoglobin levels, cancer patients had significantly lower levels of erythropoietin regardless of cisplatin therapy.

Symptoms

Cancer patients often are fatigued and a major treatable component of fatigue is anemia. In a study of 1171 patients, fatigue was identified as the leading complaint of cancer patients—greater than pain, nausea, or emesis (5). Indeed, this study found that although physicians' major focus was treating pain, patients noted that fatigue was a greater concern. In addition to fatigue, anemia may be associated with other symptoms: shortness of breath, tachycardia, chest pain, dizziness, headache, claudication pain, colonic angina, and even depression. The pattern of symptoms and the individual's ability to tolerate them is significantly dependent on the rapidity of onset of the anemia, the patient's baseline functional status, and comorbid conditions. Although anemic patients may show pallor, orthostasis (if insufficient volume expansion has occurred), and hypoxia, these are usually patients with large acute hemorrhages who have not had sufficient time for volume expansion. It is the gradual onset of anemia that is much more characteristic of oncology patients and is more often associated with the insidious symptoms of fatigue, decreased exercise tolerance, and, in the elderly, sometimes confusion. Indeed, elderly patients have a lower reserve capacity and may display any of these symptoms at higher hemoglobin levels. A number of patient self-assessment scales have been created in the past decade by Cella to assess the effect that anemia has on the quality of life (QoL) in the individual patient (5). These scales concentrate on both the fatigue related to anemia with measurements of weakness, energy level, social limitations, and nonfatigue-related symptoms including difficulty walking, dizziness, headaches, dyspnea, chest pain, libido, and difficulty with motivation.

With laboratory testing, the diagnosis of anemia is rarely difficult. The history and examination clarifies how well a patient is tolerating the anemia. Physical examination findings are highly variable. Pallor can be difficult to recognize and is very dependent on pigmentation but mucosal membranes, nail beds, and palmar creases are often areas where pallor is more consistently noted. The decreased volume of anemia may cause widened pulse pressure, a hyperdynamic precordium, and systolic flow murmurs loudest at the apex with radiation along the sternum to the neck. Finally, patients with severe anemia can show signs of high output cardiac failure with peripheral edema and an S_3 gallop.

Transfusion

Despite a decade of debate, the question remains: What level of anemia is clinically significant? Oxygen delivery is maximized at hematocrits between 30% and 40%, but observational studies have shown no difference in morbidity and mortality in patients with hematocrits as low as 10%, provided sufficient intravascular volume is maintained. In the intensive care medicine literature, there remains a debate over what transfusion threshold should be used. A recent multicenter randomized trial of 838 intensive care unit patients showed that a restrictive transfusion strategy, using 7 g/dl of hemoglobin versus 10 g/dl in the control, yielded similar 30-day mortality rates and had statistically significant lower inhospital mortality (6). In a later subgroup analysis, those patients with coronary disease also had similar mortality rates within the two transfusion regimens (7). Reasons for equivalent mortality despite increased oxygen delivering capacity at higher hemoglobin levels may relate to a theorized immunosuppression that some have noted with transfusions, as well as the risks of transfusion reactions and complications.

This intensive care population is very different from the patients usually seen in oncology. The cancer patient often has a chronic anemia, and the focus is generally not on shortterm mortality but rather on QoL and symptom management. It has been thought that chronically anemic patients fare better than others through compensatory mechanisms of maintenance of plasma volume, maintained cardiac output, and shifts in the oxygen-hemoglobin dissociation curve from 2,3-diphosphoglycerate production. This has been the general teaching for some time. However, there is now mounting evidence that oncology patients with chronic anemia may significantly benefit from hemoglobin levels near normal, which are far greater than that we have sought to maintain in the past or in other patient populations.

The decision to transfuse a patient with blood products must take into consideration the degree of physiologic stress from the anemia, comorbid illness, the potential of recovery without transfusion, and finally, transfusion risks. Traditionally within oncology, anemia was noted but not treated. Due to reactions and infectious risks, transfusions were reserved to those times when patients were thought to substantially benefit from exposures to these risks. Transfusion thresholds varied but were often carried out only when hemoglobin levels dropped substantially, sometimes below 8 g/dl. New data suggest that QoL may be better maintained at much higher hemoglobin levels, and that some patients may be undertreated.

Immunologic Effects of Red Blood Cell Transfusion

The effect of transfusion on immunologic function has been debated for three decades. In 1973, Opelz et al. described an improvement of allograft survival in patients who had previously received transfusions (8). Allogeneic transfusions have also been shown to improve disease response in patients with inflammatory bowel disease. Each of these suggested a potential immunomodulatory effect of allogeneic transfusions. However, this enthusiasm has been tempered by concern for the impact this may have on those requiring transfusions for hematologic support, particularly in oncology patients undergoing surgery with curative intent.

In the 1980s, a number of retrospective analyses suggested that patients who received blood products perioperatively for cancer-related surgery had increased incidence of tumor recurrence. There were also several conflicting studies that did not support an immunosuppressive theory. These were retrospective studies, many of which are plagued by multiple confounders. A meta-analysis by Chung et al. (9) compiling over 5000 patients undergoing colorectal carcinoma surgery concluded that there was an increased risk for adverse outcome (death, cancer death, or recurrence) in transfused patients (odds ratio of 1.69). In a similar meta-analysis, transfused patients with colorectal carcinoma had a relative risk of recurrence or cancer-related death of 1.37 (10). Again, these analyses were limited by the data of the individual studies, which could not sufficiently correct for confounders such as comorbidities.

There have been two randomized trials that evaluated allogeneic transfusions and the risks for infection and tumor recurrence. Busch et al. (11) randomized 475 patients to autologous and allogeneic transfusion perioperatively for colorectal carcinoma resection. There were no substantial differences between the two groups for postoperative mortality, infectious complications, recurrent disease, or disease-free survival, but there was an increase in disease-free survival in patients receiving no transfusions (73% vs. 59% in those receiving transfusions). However, 28% of those assigned to the autologous group also received allogeneic transfusions because a two-unit limit was set for autologous transfusions. This may have diluted the power to detect changes due to allogeneic transfusions. A second study also failed to show a difference in survival due to transfusion (12).

The mechanism behind a hypothetical immunosuppression from allogeneic transfusions has not been fully explained. It may involve an alteration in the cytokine milieu, with down-regulation of cell-mediated immunity accounting for the enhanced tumor survival as well as the improvement that has been noted in inflammatory bowel disease (12). Heiss et al. confirmed that allogeneic blood transfusions do indeed alter cytokine production in a study of 52 patients undergoing colorectal surgery who required transfusions. Patients receiving allogeneic transfusions had increased levels of interleukin-2 (IL-2) and IL-2 receptors, lower levels of tumor necrosis factor, and significantly elevated IL-10 levels. This again supports an immunomodulatory role of transfusions, which may place patients at increased risk for infection and tumor recurrence through a less vigilant immune system following transfusion.

Erythropoietin

There has been rapid progress during the last two decades as biotechnology has changed our options for treatment of anemia. It was only in 1985 that recombinant human erythropoietin (rHuEPO) was purified and cloned. In 1987, it was approved for treatment of anemia related to renal disease and then, in 1990, it was approved for human immunodeficiency virus (HIV)–related anemia. A number of small phase I and II trials in the early 1990s showed efficacy in the treatment of anemia related to chemotherapy. Ludwig et al. (13) showed in a phase II trial of 13 patients with multiple myeloma–related anemia an 85% response rate to epoetin alfa treatment with at least a 2 g/dl increase in hemoglobin and relief from transfusion dependence. Similarly, in a phase I–II trial of 21 patients receiving cisplatin with hemoglobin levels less than 11 g/dl, patients were randomized to 100 units/kg or 200 units/kg five times per week and the overall response rate was greater than 50%, with a mean rise in hemoglobin of 2.5 g/dl (14).

In a randomized trial of erythropoietin, Abels (15) studied 413 patients with a variety of advanced malignancies (excluding myeloid malignancy) and hematocrits less than 32%. Patients not receiving chemotherapy were given erythropoietin at 100 units/kg subcutaneously three times weekly while patients undergoing chemotherapy were given 150 units/kg three times weekly, with each group titrated to keep hematocrit less than 38%. In the nonchemotherapy group, 32% of those treated with erythropoietin had an elevation in hematocrit of six or more points, after 8 weeks, compared with 10% in the placebo group. Those undergoing nonplatinum-based regimens had a higher response rate (58% vs. placebo 13%) compared with cisplatin-treated patients (48% vs. placebo 6%) at 12 weeks. No increased rate of adverse effects was noted in erythropoietin groups, and QoL parameters showed improvement in all patients responding to erythropoietin regardless of chemotherapy treatment. At the end of the first month, transfusion requirements for rHuEPO patients had already decreased again regardless of the chemotherapy regimen.

Based on the data from these phase I and II trials, erythropoietin was approved for treatment of chemotherapyassociated anemia in 1993. However, it had not yet been shown to be effective in large trials with a large variety of tumor types. Three large community-based, observational studies were completed during the last 5 years (Fig. 67-1). Each prospectively examined the open-label use of erythropoietin in anemic cancer patients undergoing chemotherapy and recorded change in hemoglobin, transfusion requirements, and QoL measurements. All three studies reached similar conclusions regarding the effectiveness of erythropoietin in increasing

both hemoglobin levels and QoL scores.

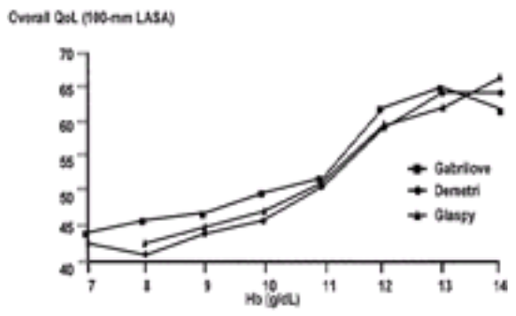

FIGURE 67-1. Community-based trials. Overall quality of life (QoL) associated with hemoglobin (Hb) levels (cross-sectional). LASA, Linear Analog Scale Assessment, also known as Cancer Linear Analog Scale (CLAS). (From references 16,17 and 20, with permission.)

Demetri et al. (16) examined 2370 patients with nonmyeloid malignancies, the majority (78%) of whom had solid tumors (24% lung, 17% breast, and 13% gynecological). Roughly one-fourth of these patients received a platinum-based therapy—a regimen known to cause significant anemia. Each had a hemoglobin level less than 11 g/dl, with an overall mean hemoglobin of 9.3 g/dl, and were given 10,000 units of epoetin alfa three times weekly with increased doses to 20,000 units if unresponsive at week four. Sixty-three percent of patients responded by an increase of at least 1 g/dl after 4 weeks of treatment. At 4 months, the mean hemoglobin had risen by 2 g/dl, and the transfusion rate had decreased from 29% the month before treatment to 5% at month four. Also, patients showed an improvement in QoL as measured by visual analog scales and by the Functional Assessment of Cancer Therapy-Anemia, self-report instruments. The difference was statistically different ($p < .001$), with those with the greatest increase in hemoglobin showing the most improvement. Those with a less than 2 g/dl response had improvement in QoL measurements if the disease was stable or responsive to chemotherapy. As might be expected, patients did not have an improvement in QoL if hemoglobin level did not increase or if they had disease progression. However, those with progressive disease and a greater than 2 g/dl response showed a much less severe decrease in QoL compared to similar patients that had no improvement in hemoglobin level.

These results were consistent with a similar study by Glaspy et al. (17). This open-label, nonrandomized study enrolled more than 2352 patients with hematologic or solid tumor malignancy under the care of more than 500 community-based oncologists. Epoetin alfa was well tolerated, with only a 3% discontinuation rate from side effects. More than half of those patients evaluable had an increase in hemoglobin level of greater than 2.0 g/dl. There were insufficient data to determine if there was survival benefit in those receiving epoetin alfa therapy and to fully differentiate QoL improvements by tumor response, although trends showed improvements in those with complete, partial response, or even stable disease. This study also showed decreased transfusion requirements (by 50%) and again no easily identifiable predictors for response. Some studies have shown that early changes in the transferrin receptor protein level, reticulocyte count, and hemoglobin may be the most effective way to identify those who are responding early in the course of treatment, but these have not yet been shown to be an effective clinical tool (18). Other measurements of endogenous erythropoietin levels and ferritin levels have had inconsistent abilities to predict response.

The three-times-weekly regimen for epoetin alfa administration is somewhat restrictive. Patients or their caregivers must either learn to administer injections or make frequent visits to the clinic, increasing the cost of care. There is clinical evidence showing efficacy of a once weekly dosing schedule. In a study of 62 healthy, nonanemic male volunteers, Cheung et al. (19) administered several doses and dosing regimens, including a study randomizing patients to either 150 IU/kg 3 times a week for 4 weeks or 600 IU/kg once per week for 4 weeks. Results from these trials showed that epoetin alfa's pharmacologic response is dependent both on the dose and dosing regimen. Both the three times weekly and the once weekly dosing regimens maintained elevated serum erythropoietin levels and reticulocyte percentages (1–2%) (19). This finding suggested that weekly dosing, which is more convenient and likely more cost-effective, may be an option in the treatment of patients with cancer-related anemia.

Gabrilove et al. examined this issue in the third of the large community-based trials of erythropoietin (20). Patients were dosed at 40,000 units per week with a dose escalation to 60,000 units/week if unresponsive. Again, weekly epoetin alfa offered significant improvements in QoL, hemoglobin level, and transfusion requirements, which was identical to the results in the two previous, community-based trials using three times a week schedule. This large study provided reassuring clinical data that once weekly dosing is a reasonable alternative, and it has now become the community standard in the United States.

Prevention of Chemotherapy-Induced Anemia

Although the above studies all showed that it was possible to treat anemia resulting from chemotherapy treatment, none examined the outcomes associated with the prevention of anemia. In 1997, a blinded study randomized 27 patients with small cell lung cancer receiving treatment with cyclophosphamide, doxorubicin, etoposide, and granulocyte colony-stimulating factor (G-CSF) to receive placebo or epoetin alfa (at 75 units/kg/day beginning on day 1 continuing through six cycles) (21). Crossover to the treatment arm was allowed for placebo patients who became anemic. This chemotherapy regimen had previously resulted in a 100% anemia rate and 80% transfusion dependence. In this study, those randomized to erythropoietin had a mean time to anemia of 3.7 cycles compared to 1.5 cycles of placebo patients. Time to transfusion was 96 days for those treated with epoetin alfa compared with 43 days for placebo patients. Although impressive differences in time to transfusion were seen, because of crossover, further effects of epoetin alfa may have been blunted. Similar preventative results were found in a trial of 36 patients with head and neck carcinoma receiving neoadjuvant chemotherapy with paclitaxel and carboplatin. The mean hemoglobin of the erythropoietin group fell 0.5 g/dl while those receiving no treatment had a decrease of 3.3 g/dl (22).

Anemia and Treatment Response

A number of studies have shown that tumor hypoxia reduces the tumor responsiveness to radiation therapy. It is thought that oxygen is required to prevent cellular repair of DNA damage from hydroxyl ions produced from radiation. These oxygen molecules fix the damaged areas, preventing repair of sublethal damage from radiation. Not surprisingly, the radiation dose required to kill cells in a hypoxic environment is significantly higher than those with an adequate oxygen supply. Brizel et al. have shown that patients with head and neck tumors treated with radiation therapy have lower, 2-year survival (70% vs. 31%) and 2-year local tumor control (82% vs. 41%) if the PO_2 within the tumor site is less than 10 mm Hg (23). Likewise, differences in survival based on hemoglobin level have been shown in non–small cell lung cancer (hgb >13), and in bladder, prostate, head and neck, and anal cancer (24). Although no current trials have been published showing that using epoetin alfa to increase hemoglobin levels will increase tumor responsiveness to radiation therapy, the above studies suggest that it is fertile ground for further investigation. A recent trial of erythropoietin in the treatment of chemotherapy-related anemia included survival as a secondary end point (25). This trial confirmed other studies showing correlation between improvement in hemoglobin levels and QoL scales. It also showed a trend towards improved survival in its study of 375 solid and hematologic cancer patients randomized to epoetin alfa or placebo. Although not reaching clinical significance, mean survival in the epoetin alfa group was 17 months, compared to 11 months in those patients treated with placebo ($p = .13$). This must be tested further before adding survival to the list of epoetin alfa's benefits.

Novel Erythropoiesis-Stimulating Protein

Novel erythropoiesis-stimulating protein (NESP) (darbopoietin alpha) is an analog of erythropoietin with two additional oligosaccharide chains; it is a larger molecule (38,500 daltons vs. 30,400 daltons) with a slightly different amino acid structure. With the increased glycosylation, its half-life is far greater. Intravenous administered NESP's half-life measures 25.4 hours, and the subcutaneous halflife is even longer at greater than 48 hours (26). Although its affinity for the erythropoietin receptor is somewhat less than rHuEPO's affinity, this does not seem to affect its effectiveness. Two small multicenter studies have shown NESP's efficacy in dialysis patients when given either intravenously or subcutaneously. Weekly administration and three-times-weekly administration (with same total dose) were compared, with no difference in responsiveness between the two arms; the mean change in hemoglobin in the subcutaneous arm was 1.08 g/dl at 4 weeks. The optimal dose was 0.45 µg/kg given weekly based on a dose escalation phase of the study (27). In preliminary studies, Glaspy et al. has compared NESP given weekly to epoetin alfa given three times weekly with no significant difference between the two regimens in oncology patients (28). In a dose escalation trial (29), the highest dose of 4.5 µg/kg gave a mean increase in hemoglobin level of 2.6 g/dl at the trial's end. Further trials are ongoing to determine the optimal dose and schedule of this new agent, and randomized trials comparing NESP to epoetin alpha in the oncology patient are eagerly awaited.

In the future, blood substitutes may play a role in the management of the oncology patient. At present, however, they have not been sufficiently studied, continue to have significant barriers to use, and remain only an intriguing promise. As safety and efficacy improves and use begins in other disciplines, such as surgery, we will begin to see more investigation in the use in oncology patients.

NEUTROPENIA

One of the most common, dose-limiting toxicities of chemotherapy regimens remains neutropenia and its associated complications. Febrile events during neutropenia may be as high as 10% per day for neutropenic patients. Mortality as a consequence of neutropenia may still be as high as 3% in patients with solid tumors (30). Although supportive care for neutropenia continues to be aggressive, with broadspectrum antibiotics and hospitalization for those at moderate to high risk, newer outpatient oral antibiotic regimens have been shown to be appropriate in certain lowrisk populations (31). In addition to the infectious risks, neutropenia often further complicates treatment by requiring dose reductions and dose delays, the consequences of which are difficult to discern.

There are three growth factors with demonstrated efficacy currently available, and a fourth, promising, secondgeneration growth factor is currently awaiting approval in the United States. Filgrastim *(E. coli* derived G-CSF), sargramostim (yeast-derived granulocyte-macrophage colonystimulating factor [GM-CSF]), and molgramostim (*E. coli* derived GM-CSF) all enhance proliferation and maturation of myeloid cells. G-CSF is a lineage-specific growth factor that hastens maturation and release of the committed progenitor pool and prolongs circulation of released granulocytes. The growth factor also enhances neutrophil efficacy through increases in chemotaxis and phagocytosis and primes granulocytes for respiratory burst. With stimulation by growth factors, progenitor cell production and maturation of neutrophils may occur within a single day, compared with the usual 5-day maturation process.

GM-CSF is a lineage-nonspecific factor that acts synergistically with other cytokines to enhance erythroid and multipotent colonies, with resulting broader hematologic effects. Clinical effects include expansion of the myeloid, eosinophil, and monocyte/macrophage pools as well as increased neutrophil activity similar to G-CSF's effects.

G-CSF and GM-CSF are administered subcutaneously at standard doses of 5 μg/kg/day and 250 $\mu g/m^2$/day, respectively; lower doses of G-CSF are now being studied and may lead to more cost-effective administration. Use of these growth factors concomitantly with radiation and chemotherapy is not recommended due to potentially increased toxicity. The optimal timing for initiation and duration of therapy is not completely clear, but typically, growth factor is begun 1–3 days after completion of chemotherapy and discontinued after post-nadir neutrophil recovery. Toxicity related to G-CSF is generally mild. Up to 40% of patients complain of medullary bone pain. Infrequent reactions include allergic reactions, Sweet's syndrome, infection site reaction, and reduction in platelet counts. GM-CSF has a broader range of side effects; patients may note fever, nausea, headache, bone pain, diarrhea, thrombosis, and anorexia.

The data examining the role of growth factors in oncology patients are quite substantial. The American Society of Clinical Oncology (ASCO) periodically reviews the literature and updates its evidence-based recommendations for clinical practice (32). Although there is much variation in the use in individual cases, these guidelines help form a basis of clinical practice. The use of G-CSF in cancer treatment must be considered in three individual circumstances— primary and secondary prophylaxis of neutropenia and treatment of neutropenic fever (Table 67-1).

Primary prophylactic use should be reserved for those patients with expected incidence of febrile neutropenia of >40%. Primary prophylaxis should not be used in most patients receiving most standard chemotherapy regimens.
Special populations: Certain populations that are at higher risk for infectious complications because of bone marrow compromise or other complications may be considered for primary prophylaxis.
Secondary prophylactic use: Dose reduction can be considered rather than CSF use in those with previous febrile neutropenia or prolonged neutropenia.
Treatment: CSFs should not be used to treat afebrile neutropenia or in cases of uncomplicated febrile neutropenia. Those high-risk patients with profound neutropenia, sepsis, or documented infection may benefit from adjuvant treatment with CSFs.
Acute myeloid leukemia: CSFs can be used to decrease the duration of neutropenia following induction chemotherapy and possibly following consolidation.
Radiation: CSF use should be avoided in those receiving concomitant chemotherapy and radiation.

From Goldman M, Juodvalkis S, Gill P, et al. Hepatitis C lookback. *Transfus Med Rev* 1998;12(2):84–93, with permission.

TABLE 67-1. AMERICAN SOCIETY OF CLINICAL ONCOLOGY GUIDELINE HIGHLIGHTS FOR COLONY-STIMULATING FACTOR (CSF) USE

Primary Prophylaxis

Several large prospective trials have shown the ability of G-CSF to reduce the incidence of febrile neutropenia in regimens with rates of neutropenia approaching 40% (33,34 and 35). In these studies, febrile neutropenic incidence was reduced by half in patients receiving growth factor support. Additional studies have confirmed the efficacy of growth factors in preventing neutropenia but unfortunately no study thus far has shown improvement in disease-free or overall survival in patients receiving growth factors. Bokemeyer et al. (36) showed that high-risk patients with testicular cancer were able to tolerate the full course of chemotherapy with G-CSF support, but there was no difference in overall survival. Similar results have been shown in non-Hodgkin's lymphoma, small cell lung cancer, and in breast cancer. ASCO recommends primary prophylaxis for regimens that have neutropenic fever rates of greater than 40%. However, few routinely prescribed chemotherapy regimens lead to this degree of myelosuppression. This recommendation was based on original data that showed cost effectiveness at neutropenic fever rates of 40%. More recent data from Lyman et al. suggest that a lower threshold of 20% may be considered when all costs of care are considered (37). Regardless of the threshold considered, it is important to not only consider the regimen being used but also whether or not the patient being treated is at higher risk for febrile neutropenia and its complications.

Special Populations

Although few standard regimens induce neutropenia at sufficient rates to warrant primary prophylaxis, there are a number of populations whose risk may warrant special consideration. Elderly patients, HIV patients with lymphoma, and those with significant comorbidities have been cited as special populations for whom primary prophylaxis should be considered. Rates of neutropenia in treatment regimens for non-Hodgkin's lymphoma varied between 21–47% in a number of studies of elderly patients. Even more important, risk for infectious death can be up to 30% in these patients with the majority occurring following the first cycle of chemotherapy. Therefore, a less stringent standard may need to be considered for older and sicker patients. Other populations recognized by the ASCO committee that may benefit from prophylaxis are those with extensive previous chemotherapy or radiation and those in whom there may be significant increased risk of infection. Indeed, the ASCO guidelines recommend that clinical discretion prevail in cases in which the clinical risk of neutropenia is judged to be substantial.

Secondary Prophylaxis

Because of the difficulty in identifying high-risk patients for primary prophylaxis, the most common current clinical practice is secondary prophylaxis. This is a population of patients who have already proven themselves to be at high risk for neutropenic fever and its adverse effects by a first episode of neutropenia. In a study of patients receiving cyclophosphamide, doxorubicin, and etoposide for advanced small cell lung cancer, Crawford et al. showed that in patients with previous febrile neutropenia, the use of G-CSF reduced the duration of febrile neutropenia in subsequent cycles (from 6 days to 2.5 days) and the rate of this complication (from 100% to 23%), even when maintained on the same dose (31). Thus, prophylaxis allows for maintenance of dose intensity, which may or may not yield improvements in outcome. Although the concept that maintaining dose intensity and schedule leads to improved survival seems reasonable, is suggested by retrospective studies, and is consistent with current strategies, there have been no definitive studies that prove this. Because of this lack of data, the ASCO committee on growth factor use has suggested that dose reduction also be considered as an alternative to secondary prophylaxis with colony-stimulating factors (CSFs) in the absence of evidence that dose intensity improves outcome (32). The relationship between dose and outcome will continue to be an area of clinical investigation and clinical decision making for years to come.

Treatment of Febrile Neutropenia

Thus far, a number of well-designed prospective trials have examined the use of CSFs to treat those who already have febrile neutropenia. Although a number have shown a decrease in the duration of neutropenia, none has shown a decrease in infectious consequences and mortality. A pediatric study by Mitchell et al. showed a mean decrease of 2 days in hospitalization and neutropenia, and 1 day in antibiotic therapy in those receiving G-CSF (38). A study of 68 febrile neutropenic patients by Ravaud et al. (39) suggested that GM-CSF reduced the duration of neutropenia, hospitalization, and antibiotic use. However, the mean decrease in hospitalization was only 1–1.5 days.

Despite evidence that CSFs can shorten febrile neutropenic episodes, it is unclear if those with uncomplicated neutropenic fevers should receive this support. However, the ASCO guidelines do recognize that there are populations that are at risk for a particularly poor outcome and should obtain CSF. These include those with profound

neutropenia (absolute neutrophil count £100/µl), sepsis, invasive fungal infection, pneumonia, and uncontrolled disease.

Use of Colony-Stimulating Factors in Hematologic Malignancies

There was much initial concern over the use of CSFs in leukemias because of possible stimulation and regrowth of leukemic cells. These patients have the highest incidence, and frequently the longest duration, of neutropenia, and CSF, if safe, would presumably have the greatest potential benefit through decreasing hospitalization time, antibiotic use, and neutropenic complications. A number of studies have now shown the safety and efficacy of CSFs in patients with acute myeloid leukemia (AML) (40,41). Although only one study (42) has shown improvement in response rates due to CSF use, there is consensus that CSF use can improve time to recovery of neutrophil counts without enhancement of leukemic growth. A study from the Southwest Oncology Group study randomized 234 patients with AML who were over the age of 55 to placebo or G-CSF (400 µg/m^2) daily until recovery (43). The G-CSF treated group had a 15% reduction in duration of neutropenia (for a mean reduction of 3 days), 2 fewer hospital days with fever, and 4 fewer days of intravenous antibiotics. However, as in the previous studies, there was no significant statistical difference in response rates, documented infections, or overall survival. Therefore, use of CSF is safe and may be indicated in certain patient populations at high risk for complications from febrile neutropenia.

Pegylated Filgrastim

Although efforts are still under way to better define the appropriate uses of G-CSF, several difficulties with its administration still exist. The daily administration of G-CSF in the clinic setting can be both expensive and inconvenient to patients. A longer-acting form of granulocyte stimulating factor has been developed and tested. A conjugate with a 20 kilodalton polyethylene glycol attached to the N-terminus of the standard recombinant human G-CSF molecule, SD/01 has a prolonged half-life with no apparent change in its pharmacodynamics. Due to the elimination of renal clearance of this larger molecule, SD/01 levels at the neutrophil remain elevated until absolute neutrophil count levels begin to rise and are then cleared by receptors on the neutrophil itself. This self-regulation allows dosing once per chemotherapy cycle, reducing inconvenience and, hopefully, overall health care costs. Several early clinical trials have confirmed this promise. In a trial of patients with non–small cell lung cancer, patients were randomized to G-CSF or SD/01 at one of three different doses. Results were comparable between standard G-CSF and the pegylated version, and a dose-response was seen (44). In a recent blinded and randomized phase III trial of 310 patients with breast cancer, SD/01's efficacy was compared with that of filgrastim in the primary prevention of neutropenia (45). The duration of neutropenia was similar in each group—1.7 days in those treated with SD/01 vs. 1.6 days in filgrastim patients. The incidence of febrile neutropenia was 9% in SD/01 patients and 18% in filgrastim patients.

THROMBOCYTOPENIA

Platelet Transfusions

Decreased platelet counts are common in the cancer patient; the causes include invasion of the marrow by tumor, nutritional deficiencies, myelosuppression due to cytokines from the tumor, and myelosuppression/myeloablation from intensive chemotherapy regimens. Thrombocytopenia was originally a common complication of acute leukemias and their treatment, but it is now an increasing complication of solid tumor treatment as multiagent chemotherapy is adopted in a variety of malignancies, including lung and lymphoma.

Although mortality from major hemorrhages in an oncology patient is increasingly rare, thrombocytopenia is a frequent concern for the oncology patient. Complications vary from harmless ecchymoses and petechiae to disruptive epistaxis and gingival bleeds, to life-threatening gastrointestinal and intracranial hemorrhages. There is a perception that diffuse mucosal hemorrhages are frequent in patients with severe thrombocytopenia. However, Chu et al. (46) showed in a study of 133 patients with various levels of thrombocytopenia that specific sites (either unifocal or multifocal) were usually responsible for hemodynamically significant bleeding. This indicates that thrombocytopenia often unmasks areas of bleeding rather than causes diffuse mucosal bleeding (it should be noted that this study is somewhat dated and may or may not apply to patients undergoing bone marrow transplantation).

Whether the patient has simple petechiae or a major hemorrhage, the treatment for thrombocytopenia is still the same: prevent or treat the hemorrhage by supplementing the platelet level. More than 9 million platelet units were transfused in 1997, and oncology patients consumed as much as one-third of these transfused platelets. While most platelets transfused in the surgical patient are one-time transfusions in direct response to bleeding episodes and increased consumption of platelets, much of that used in the oncology patient is given for prophylaxis, with multiple transfusions required over longer periods of time. Prophylactic platelet transfusions are common, frequent, and are now considered the standard in the care of oncology patients. However, the standard at which one should transfuse has shifted over the last decade. As late as 1992, 80% of physicians sampled were using a standard threshold for prophylaxis of 20,000/µl (47). Based on recent studies, the last ASCO committee on platelet transfusions now recommends the new threshold of 10,000/µl at which to transfuse oncology patients (Table 67-2).

10,000/µl should be the prophylactic threshold for adult patients with adult leukemia and most solid tumors.
20,000/µl should be considered for some tumors that, due to tumor necrosis, are particularly at risk for bleeding. Examples include melanoma, bladder, gynecological, and colorectal tumors.
Platelet counts greater than 50,000/µl should be reached before surgery.
To reduce alloimmunization, leukoreduced blood products should be used in patients who will require continued platelet transfusions.
Patients refractory to platelet transfusions should be treated with HLA-matched platelets.

From Schiffer CA, Anderson KC, Bennett CL, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19(5):1519–1538, with permission.

TABLE 67-2. AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLINICAL PRACTICE GUIDELINES FOR PLATELET TRANSFUSIONS

The earliest data came from Gaydos et al. (48), who showed an inverse relationship between bleeding episodes and platelet levels. At 20,000 platelets/µl, the percentage of hospital days with hemorrhage was 4%; with 10,000/µl, the percentage was 8%, and even greater levels of bleeding were observed at <5000/µl. While not finding an absolute cutoff at which bleeding occurs, Gaydos et al. did note multiple risk factors that make bleeding more likely. These included infection, fever, the underlying disease process, and drugs that interfere with platelet function (including aspirin, which was used as an antipyretic in many of these patients). Despite little evidence to show that 20,000 platelets/µl was indeed the level at which bleeds became more common, it was eventually adopted as such. Since then, there have been one retrospective and two prospective trials of prophylactic transfusions comparing 20K to 10K as the threshold for transfusion.

Gmur et al. (49) retrospectively examined 102 patients with leukemia over a 10-year period. Patients received transfusions at a threshold of 5000/µl. Those with a fever or minor bleeding had a threshold of 10,000/µl, and those who required heparin or an invasive procedure had a threshold of 20,000/µl. There was little difference in significant bleeding episodes between the three groups. There were three episodes of fatal hemorrhagic episodes, but these occurred at higher platelet levels. Again, a threshold below which bleeding was more likely was still not clearly identified.

More recently, Heckman et al. (50) randomized 78 acute leukemia adult patients to prophylactic transfusions at either 10,000/µl or 20,000/µl level during induction chemotherapy. Patients all underwent 1 of 3 different chemotherapeutic regimens, with exclusion criteria of uncontrolled infection, history of bleeding diathesis, disseminated intravascular coagulation, acute promyelocytic leukemia, AIDS, and platelet refractoriness. There were no statistically significant differences between platelet refractoriness or bleeding episodes. No fatal bleeding events occurred in either group during the study, but there were eight transfusion reactions in the 20,000/µl threshold group compared with none in the 10,000/µl group ($p = .005$). Patients with the lower threshold did receive more prophylactic and total transfusions [mean of 10 vs. 6 transfusions for prophylaxis and mean of 11 vs. 7 for total transfusions (nearly statistically different)]. The study was powered to show a difference of 25% increase in bleeding episodes with a standard incidence of 70%; the actual bleeding incidence was 90%. Thus the study should have adequately noted any differences in bleeding events.

A larger multicenter trial was soon performed, which confirmed this earlier data. Rebulla et al. (51) used similar thresholds in 255 adolescent and adult patients with AML (excluded acute promyelocytic leukemia). During episodes of fever to 38°C, active bleeding, or invasive procedures, the high threshold was used (this occurred 22.6% of the time). Major bleeding episodes were similar in the two groups with 21.5% (10,000/µl group) and 20% (20,000/µl) of patients having episodes greater than petechiae, mucosal, or retinal bleeding ($p = .41$). One fatal bleed, a cerebral hemorrhage, did occur in the lower threshold group, but this event occurred when the platelet count was 32,000. Platelet transfusions were 21.5% lower in the 10,000/µl threshold group ($p = .001$). Gastrointestinal bleeding did occur twice as often (12

episodes vs. 5 episodes) at the more restrictive threshold, but there were no differences in the number of red cell transfusions required due to this.

Procedures

Bishop et al. (52) showed that the thrombocytopenic patient can undergo major surgery provided that adequate transfusion support is given. The retrospective analysis of 95 patients with acute leukemia requiring a variety of surgeries showed that, provided counts exceed 50,000, blood loss is usually minimal. Seven percent of those undergoing surgery had >500 ml of blood loss, and only 7% required more than four units of packed red cells. There were no surgically related fatalities. As many as 66% of the patients in the 167 operations performed were neutropenic at the time of surgery, but there were no postoperative infections attributable to the surgical intervention. Based on this, the ASCO committee recommended a threshold of 50,000/µl before major invasive procedures (53). There is little guidance in the literature regarding the appropriate levels before lumbar puncture or bone marrow aspiration. Several retrospective studies of no more than 20 adult patients have recommended transfusions before lumbar puncture for levels of less than 20,000, but this has not been examined in larger trials.

Refractoriness

Refractoriness to platelet transfusion is a common and significant effect of repeated transfusions and may be as high as 35% in patients with AML (54). Refractoriness to platelet transfusion is thought to be due to platelet-reactive alloantibodies against histocompatibility antigens. These antibodies consume large numbers of transfused platelets and leave little to show for the transfusions.

It is now recognized that leukocytes contaminating the platelet transfusion play a role in immunization. Because platelets lack class II histocompatibility antigens, another agent must serve as a costimulant along with its class I antigens. Several methods are used to reduce leukocytes within a transfusion. Filtration is the older process but varies in its ability to filter leukocytes; it usually results in a three log reduction in the volume of leukocytes. Newer methods have used ultraviolet light to reduce antigenicity of transfusions. In the Trial to Reduce Alloimmunization to Platelets, over 600 patients were randomized to receive either pooled, filtered, single-donor filtered, or pooled irradiated platelets. Each of the methods to reduce the number of viable leukocytes transfused led to a reduction in the production of antibody formation compared with simple transfusion with pooled platelets (17% vs. 45%). Leukocyte-depleted transfusion products (both RBCs and platelets), therefore, should be used in leukemic patients receiving induction and consolidation. The data behind those with solid tumors who require platelet transfusions are not as clear, mostly because these patients rarely require the prolonged transfusions common in the treatment of leukemic patients. Little research has been done in this population. Leukodepleted transfusions are also less likely to cause transfusion reactions, which are thought to be mediated by cytokines from leukocytes. However, both methods of leukocyte reduction are inefficient, costing a loss of up to 25% of platelets and driving up the costs of transfusions.

Although patients who received repeated transfusion often develop antibodies, other factors also play a role in a poor response to an individual platelet transfusion. Fever, infection, and an active bleeding source all consume additional platelets and may be reflected in a less than expected response to a transfusion. The ASCO committee has recommended that following transfusions, platelet counts be measured again to determine an adequate increase in platelet counts. If a patient fails to have adequate increases in posttransfusion platelet counts in at least two ABO-compatible transfusions, the clinician should consider alloimmunization and other causes of platelet destruction such as disseminated intravascular coagulation, sepsis, and immune thrombocytopenia purpura. One can measure platelet antibody titers, but it is often not clear how this will guide clinical decision making. Often patients with alloimmunization can be transfused with HLA-matched platelets with good response (up to 50%), but it is critical that further transfusion be coordinated with blood bank personnel. If HLA-matched platelets fail to produce adequate responses, cross-matched or familymember donated platelets may then be used.

Thrombopoietic Agents

Platelet transfusions are costly, at times ineffective, and place the recipient at risk for transfusion reactions and infectious exposures. Given the promising responses of anemia and neutropenia to growth factors, it is hoped that a pharmacologic alternative to platelet transfusion will soon be found. Early efforts using cytokines to stimulate platelet production showed significant toxicities, including fevers and hypotension (IL-1) and headaches, fatigue, and fevers (IL-6), but little clinical benefit. However, IL-11 has been approved as a thrombopoietic agent based on promising data in breast cancer patients. IL-11 was originally derived from stromal cells and was found to stimulate proliferation of a murine plasmacytoma cell line. It has multiple effects on both hematopoietic cells and other organ systems such as intestinal and bronchial epithelial cells. IL-11 either alone or in concert with other cytokines has been shown to increase megakaryocyte maturation markers, megakaryocyte polyploidy, and platelet size. *In vitro* studies showed little activity alone, but *in vivo*, it has been shown to promote megakaryocytopoiesis and increase platelet production. In a study of 93 breast cancer patients, platelet transfusions were reduced in 30% of patients (55). However, side effects are significant and include edema, fatigue, myalgias, and cardiovascular events. This has limited use in general clinical practice and fueled the drive to find other agents to stimulate platelet production.

It has been less than a decade since the c-MPL ligand was identified and cloned. From this development, two variants of the c-MPL ligand have been produced and studied, showing mixed results in clinical trials. RhTPO, an intact recombinant thrombopoietin, and PEG-rHuMGDF, a truncated and pegylated human recombinant megakaryocyte growth and development factor, showed early promise in phase I trials. PEG-rHuMGDF was shown to improve platelet recovery by 1 week in patients undergoing treatment with carboplatin and paclitaxel for lung cancer (56). However, neither rhTPO or PEG-rHuMGDF has since had the remarkable clinical results seen with growth factors for other hematopoietic lineages. PEG-rHuMGDF's potential in preventing thrombocytopenia in acute myelocytic leukemia patients was examined but failed to show a decrease in days to recovery of platelet counts in patients receiving PEG-rHuMGDF following induction chemotherapy (57). Likewise, studies in autologous bone marrow transplantation and stem cell transplantation patients have also failed to show any significant reduction in the length of severe thrombocytopenia or platelet transfusion requirements. Furthermore, there has been concerning evidence of antibody production to the pegylated MGDF when injected subcutaneously. In one study, 8.9% of patients given three doses of PEG-rHuMGDF developed significant thrombocytopenia. These antibodies are thought to inhibit native thrombopoietin's effects as well by a cross-reaction, thus worsening a thrombocytopenia (58). For this reason, the manufacturer halted further U.S. clinical trials of PEG-rHuMGDF in September 1998.

The story of thrombopoietin continues. A recent phase I trial of 33 patients with breast cancer receiving autologous bone marrow transplant showed both safety and tolerance to rhTPO without any signs of neutralizing antibodies (59). This study, however, again failed to show a dose effect for escalating doses of rhTPO or improvement in time to recovery of platelet counts when compared to previous study populations.

COMPLICATIONS OF BLOOD PRODUCT TRANSFUSIONS

Transfusions of blood products are obviously a necessary component in the support of the oncologic patient. However, they are not without consequence. Hemolytic transfusion reactions occur infrequently but may be responsible for as many as 1.0–1.2 deaths per 100,000 patients transfused. A total of 34 deaths in the United States may have occurred secondary to hemolytic transfusion reactions in 1990.

Alloimmunization is the most frequent complication, with estimates of rates varying from 7–30% (60). In a retrospective analysis of 564 patients with myeloproliferative or lymphoproliferative disorders from 1987–1996, Schonewille et al. found an overall immunization rate of 9% of patients receiving long-term transfusion support, with the risk of immunization of 0.5% per each RBC unit transfused. As seen in the previous section, platelet alloimmunization is a major problem in the treatment of oncology patients. However, there is some suggestion that those undergoing chemotherapy may not produce as active a response to incompatible transfusions as others requiring transfusions, thus lowering actual alloimmunization rates in oncology patients.

Transfusion Reactions

Acute reactions occur during and immediately after transfusion and vary from the discomfort of an allergic reaction with urticaria to the life-threatening hemolysis and multiorgan system dysfunction associated with acute hemolytic reactions. Due to strict and thorough cross-matching, acute hemolytic reactions are infrequent, less than 1 per 200,000 units transfused (61), but up to 16 deaths per year may be attributable to this immunologic response to an incompatible blood product. Symptoms occur early in transfusion, often within the first 5 minutes of beginning the transfusion. However, reactions can occur several hours after transfusion. Fever, chills, and hypotension typically dominate the presentation, but reactions can include such nonspecific complaints as flushing, low back pain, dyspnea, nausea, chest pain, or abdominal pain.

The pathophysiology of this reaction is the best described of transfusion complications. Hemolysis is initiated by the action of preexisting IgG or IgM alloantibodies against major blood group antigens. IgM antibodies, usually to the ABO blood group, will fix C9 to the RBC surface, activating the complement system and causing intravascular hemolysis. IgG antibodies, often binding to the Kell or Kidd blood group antigens, lead to extravascular hemolysis with removal of affected cells by the spleen, liver, and bone marrow. The initial hemolysis is just the beginning of a cascade created as macrophages phagocytose transfused cells and release of a breviary of cytokines, including tumor necrosis factor, IL-8 and IL-1, causing the symptoms mentioned above. The reaction is actually a systemic process and effects on coagulation and renal function are often seen. The balance of the coagulation system is upset as cytokines and byproducts of RBC hemolysis are released. Platelet activation and factor XII activation from antigen-antibody interaction further increase coagulation activity. Disseminated intravascular coagulation can occur with its resulting effects, and renal dysfunction is frequent. The causes are multifactorial but may be due to microthrombi from disseminated intravascular coagulation,

hypotension from cytokine effects, such as bradykinen, or intrarenal shunting creating renal ischemia.

Laboratory evidence of acute hemolytic transfusion reaction (AHTR) includes early and rapid decrease in serum haptoglobin levels and increases in serum bilirubin, plasma hemoglobin, and urine hemoglobin peaking around 6 hours after initiation of reaction. With prompt attention and discontinuation of the instigating transfusion, AHTR need not be fatal. The transfusion must be stopped immediately, intravenous saline continued, and both the transfusion sample and the patient's serum sent for investigation. Intravenous furosemide and fluid can diminish some of the effects of the intrarenal shunting. Hemolysis can also occur due to nonimmunologic mechanisms including mechanical forces, osmotic pressure (e.g., contact with nonisotonic fluid or in G6PD-deficient transfusions in patients receiving reducing agents).

Some reactions occur up to weeks following transfusion. These are frequently asymptomatic and are usually noted by a falling hematocrit associated with positive direct Coombs, elevated bilirubin, fever, hemoglobinuria, and varying degrees of renal insufficiency occurring one to weeks following transfusion. These outcomes are usually secondary to an amnestic response to RBC antigens, but may be due to *de novo* development of IgG antibodies to non-ABO antibodies. Kidd and Duffy system antibodies are more likely to result in symptomatic reactions. Treatment is usually supportive, but in cases of trauma-related massive transfusions, additional transfusions may be warranted.

Delayed hemolytic transfusion reactions tend to be less fulminant and manifest by falling hematocrits with elevated bilirubin, fever, hemoglobinuria, and a positive Coombs test seen 5 to 10 days following transfusion. Usually asymptomatic and undetected, some prospective work has shown that the actual incidence may be as high as 0.5%. More significant reactions may lead to renal failure, jaundice, and further deterioration of an already ill patient. The likely precipitating event of the reaction is an amnestic response to RBC antigens or *de novo* development of non-ABO antigens. Anti-Kidd and Duffy antibodies may play a role in those clinically significant reactions, but these are difficult to detect. Management is symptomatic support.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is a rare but life-threatening acute noncardiogenic pulmonary edema with symptoms similar to adult respiratory distress syndrome. Patients experience tachypnea and dyspnea and exhibit bilateral pulmonary edema. Differing from cardiogenic edema and cases of fluid overload, the etiology is thought to be donor HLA antibodies reacting with recipient neutrophils. These activated granulocytes are sequestered in the pulmonary vasculature, where they wreak havoc, releasing proteolytic enzymes that damage the microvasculature. Pulmonary leak then occurs, allowing fluid and protein to fill the alveoli. TRALI often occurs early in transfusion, within 2 hours, but has been reported much later. Respiratory compromise typically lasts several days, and most recover without lasting sequelae. However, some patients require short-term ventilator support. Mortality rates have been reported as high as 6%. There is no method of predicting which transfusions will result in TRALI, although multiparous women may have an increased frequency of antibodies due to exposures during pregnancy and delivery.

Febrile Non-Hemolytic Transfusion Reactions

Febrile non-hemolytic transfusion reactions, the most frequently seen of transfusion reactions, is a cluster of symptoms similar to AHTR but without the specter of fatality. Patients complain of fever, chills, nausea, emesis, and/or malaise and often have a rapid increase in body temperature of 1–2°C. Although originally attributed to antileukocyte antibodies, it is now recognized that recipient's immunologic system may also contain antiplatelet or antigranulocyte antibodies that create these symptoms. In some cases, no precipitating antibody is found at all, and cytokines are thought to play the key role. As the number of leukocyte-depleted blood products transfusions have increased, the frequency of these reactions has declined. Patients can be treated with antipyretics, usually acetaminophen, for symptomatic relief.

Platelet transfusions much more frequently cause febrile reactions than other blood products. Although some are attributable to antibodies, cytokines likely play a role. Transfusions of stored platelets more frequently cause reactions perhaps due to the production of cytokines during storage. If donor-end, leukodepleted platelet transfusions are used, the incidence of febrile non-hemolytic transfusion reactions is dramatically reduced.

Anaphylaxis and Allergic Reactions

Anaphylactic reactions are infrequent, but rapid death can occur as laryngeal edema, bronchospasms, and hypotension develop from mast cell degranulation. The majority of these reactions are seen in immunoglobulin A (IgA)-deficient patients who have anti-IgA antibodies and are then transfused with products from an IgA donor. Treatment is just as in other anaphylactic reactions with corticosteroids, antihistamines, and support measures. Future reactions can be prevented by transfusing components from IgA-deficient donors or by washing packed RBCs and platelet products to reduce the possibility of transfusing IgA. Benign allergic reactions are fairly common with any transfusion product. Antigens present in the transfused products can cause urticaria. Treatment is again antihistamines, but routine prophylactic treatment is not recommended. Patients who have had previous reactions, however, are commonly treated prophylactically with each transfusion.

INFECTIOUS RISKS AND COMPLICATIONS

Bacterial Infections

Despite likely underreporting, bacterial infection accounts for approximately 15% of reported, transfusion-related mortality. Contamination generally occurs at the time of collection from skin flora of inadequately prepared donors or from asymptomatic bacteremia from the donor. Platelets have a higher incidence of contamination because storage and increased exposure from the multiple donors of pooled platelets. These units are frequently contaminated with skin flora, which then replicates with storage at room temperature. For this reason, platelet storage is limited to 5 days. Because RBCs are stored at cooler temperatures, contaminants in these products are frequently *Yersinia*, *Serratia*, *Pseudomonas*, and *Enterobacter* species, which can survive cooler temperatures. Patients frequently present with symptoms of sepsis at the time of transfusion. Hypotension and shock can develop rapidly as accumulated endotoxin is released into the recipient. Symptoms may later develop as bacteremia occurs within the host. Efforts at prevention are largely focused on improved sterile collection techniques.

Viral Infections

The safety of the U.S. blood supply has improved over recent years such that the risk of transmission of a serious viral pathogen is approximately 29 per million units (63). Yet fear of this complication is often the greatest concern of blood product recipients. Failure to detect the presence of virus in the contaminated units is largely the result of donation and testing during the “window period” shortly after the donor has acquired the infection and before serologic conversion.

The screening of blood products for the presence of HIV-1 antibodies began in the United States in 1985; in 1992 antibody testing for HIV-2 was also applied routinely. More recently, since March 1996, products have been screened for the presence of HIV-1 p24 antigen with a consequent decrease in the duration of the window period from 55 days in 1985 to 16 days in 1996. The current estimated risk of transmission of HIV via blood product transfusion is estimated to be <1 in 493,000 (63).

Infection with human T-cell lymphotrophic virus (HTLV-1) is associated with the clinical syndromes of adult T-cell leukemia/lymphoma and tropical spastic paraparesis. There is no clear clinical disease imparted by infection with HTLV-2 virus, but there is suggestion of a neurological condition similar to that of HTLV-1 infected persons. Transfusion-related tropical spastic paraparesis has been described with an incubation period of approximately 3 years. Recipient seroconversion following transfusion of a cellular component seropositive for HTLV is approximately 40% and is diminished with increasing age of the transfused component.

Hepatitis B infection becomes chronic in approximately 10% of infected patients, usually with no symptoms. A percentage of these asymptomatic carriers have undetectable levels of hepatitis B surface antigen (HBsAg) and anti-hepatitis B core antigen (anti-HBc), such that their donated units will escape detection with an estimated risk of post-transfusion hepatitis B of approximately 1 in 63,000 (62). It is possible that this represents an overestimate and that many of these infections are acquired independently of the transfusion given the high seroconversion rate in the general public.

Hepatitis C virus was first characterized molecularly in 1989; current immunoassays are directed against various viral epitopes and provide a 70-day window for detectability. Newer screening tools, such as viral polymerase chain reaction, are now available and may decrease the window following infection to several weeks. Transfusion with an infected unit of blood results in a 90% seroconversion rate, with at least 65% of patients developing chronic infection. The majority of those infected with hepatitis C go on to develop chronic liver disease. An estimated 300,000 people in the United States may have contracted hepatitis C in the 1980s through transfusion (62). Risk of transmission with transfusion is currently estimated at 1 in 103,000 transfused units that have been screened for hepatitis C antibodies.

Many other clinical infections have been related to blood transfusion, including common pathogens such as Epstein-Barr virus and parvovirus, as well as rarer illnesses such as Chagas' disease, Creutzfeldt-Jakob disease, leishmaniasis, malaria, babesiosis, and syphilis. Fortunately the transfusion-related incidence of these diseases is uncommon. Cytomegalovirus (CMV) deserves special note because of the high seroprevalence in the United States (35–80% varying by region) and the potentially devastating effects on the immunosuppressed host who acquires the infection. CMV is a leukocyte-associated virus; thus any blood product contaminated with white blood cells is capable of transmitting infection. Several studies have shown decreased rates of CMV infection in patients receiving leukodepleted blood products, but prospective trials comparing leukocyte reduced versus CMV seronegative transfusions are limited. Thus CMV-negative donors are still used as the standard of care for

those patients in whom CMV infection could be devastating, including seronegative bone marrow transplant patients.

Other Late Complications

Secondary hemosiderosis is rarely a complication in the oncology patient requiring transfusions but can frequently occur in patients with hemoglobinopathies, aplastic anemia, or severe myelodysplasia who are transfusion dependent for years. Each unit of packed RBCs contains approximately 200 mg of iron and significant hemosiderosis usually requires more than 2 g of iron surplus (100 units of transfusion products in the absence of continued bleeding). Clinical manifestations of iron overload are the direct result of iron deposition in the affected organs and most commonly include skin discoloration, gonadal failure, liver dysfunction, and diabetes. Less frequently, patients may have cardiac failure, arrhythmias, arthropathy, and even personality changes.

CONCLUSION

The discovery of the hematopoietic growth factors and their introduction into clinical practice has dramatically changed our understanding of hematopoiesis. In addition, the clinical consequences of anemia, neutropenia, and thrombocytopenia in the cancer patient have become much better characterized. Clinical practice guidelines have been developed and are continually being revised as our knowledge base increases. Meanwhile, the areas of transfusion medicine and infectious diseases have clarified the appropriate settings for transfusion support and antibiotics and the risks and benefits of these approaches. In addition, economic studies and outcome research have focused on this critical area of supportive care to help us understand the best approaches to be used for our patients. With the advent of second generation hematopoietic growth factors, further benefits are anticipated, including trials that may shift emphasis from treatment of cytopenias to more preventive strategies. In this rapidly changing area, readers are encouraged to follow the results of ongoing randomized clinical trials as well as the updates of evidence-based, clinical practice guidelines to best incorporate the use of hematopoietic growth factors, transfusions, transfusion support, and antibiotics in the clinical care of their patients.

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68

NUTRITION SUPPORT

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Malignant disease is frequently accompanied by profound weight loss and malnutrition. In fact, cancer patients have the highest prevalence of malnutrition of any hospitalized group of patients (1). In its most severe form, weight loss due to malignancy is termed the *anorexia-cachexia syndrome* and is characterized by anorexia, skeletal muscle atrophy, tissue wasting, and organ dysfunction (2). Malnutrition associated with malignancy is a poor prognostic indicator. It is associated with a higher mortality rate (3) and a higher perioperative morbidity rate in patients who have lost greater than 5% of their body weight and have a reduction in some of the indices of nutritional status (4). The indications for implementing nutrition support in cancer patients—and its safety—have been established (5,6,7,8,9,10 and 11). But the possible benefits of nutritional therapy are still contentious.

This chapter will address the following questions: What is the effect of nutrition support on the outcomes of cancer patients undergoing various treatment modalities? What is the role of nutrition support in the treatment of cytokine-mediated cancer anorexia and altered host metabolism? Are there specific nutritional supplements that take on a pharmacological role by modulating tumor cell growth? Finally, is preservation of quality of life by reduction of fatigue and other effects of malnutrition an adequate outcome of adjuvant nutritional therapy? Because of the ongoing controversies associated with these issues and ethical issues regarding nonvolitional feeding guidelines, nutrition support of the cancer patient should be emphasized in the clinical setting. Nutrition support is an integral component of comprehensive cancer care in patients who are carefully selected through the use of nutritional screening tools and for whom appropriate goals of treatment have been established.

MALNUTRITION IN THE CANCER PATIENT

Malnutrition in the cancer patient results from several mechanical and metabolic processes. The cachexia of malignancy is a complex metabolic disorder characterized by involuntary weight loss which, if not treated, often leads to death (3). Certain tumors predispose individuals to cancer cachexia. Table 68-1 depicts the frequency of weight loss among approximately 3000 cancer patients studied by the Eastern Cooperative Oncology Group. Breast cancer and sarcomas rarely resulted in significant host weight loss compared with cancers involving digestive organs such as stomach and pancreas. Patients with lung cancer or prostate cancer also demonstrated significant weight loss and malnutrition. The Eastern Cooperative Oncology Group survey demonstrated a lower morbidity and longer survival in patients without weight loss, except in cases of pancreatic or gastric cancer. Preventing weight loss by nonvolitional feeding does fully restore the difference in outcomes (12,13).

Tumor type	Number of patients	Weight loss in the previous 6 mo (%)			
		0	0-5	5-10	>10
Favorable non-Hodgkin's lymphoma	290	69	14	8	10
Breast	289	64	22	8	6
Sarcoma	189	63	21	11	7
Unfavorable non-Hodgkin's lymphoma	211	52	20	13	15
Colon	307	46	26	14	14
Prostate	78	44	27	18	10
Lung, small cell	426	43	23	20	14
Lung, non-small cell	550	39	25	21	15
Pancreas	111	17	29	28	26
Nonmeasurable gastric	179	17	21	32	30
Measurable gastric	138	13	28	29	30
Total	2918	42	23	18	16

From Dobbs WO, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Am J Med 1988;84:491–497, with permission.

TABLE 68-1. FREQUENCY OF WEIGHT LOSS IN CANCER PATIENTS

Causes of Malnutrition

Table 68-2 lists the potential etiological factors in the development of cancer anorexia. The development of malnutrition in the individual patient is usually the result of a combination of these mechanisms (14).

Direct and indirect tumor effects
Change in taste
Dysphagia
Pain
Gastrointestinal tract obstruction
Early satiety
Anorectic factors (cytokines) produced by tumor or host
Antineoplastic therapy
Chemotherapy
Radiotherapy
Anorexia/anosmia
Nausea
Mucosal/ulcerations/infections

TABLE 68-2. ETIOLOGY OF THE ANOREXIA-CACHEXIA SYNDROME

Anorexia of Malignancy

A decrease in food intake and weight loss that occur without an overt cause is referred to as the *anorexia-cachexia syndrome*. Several factors, including changes in the central nervous system, changes in taste perception due to tumor, and depression and its associated reduced physical activity, have been implicated as causes of cancer anorexia. The regulation of appetite is complex and is mediated by blood nutrient levels, host nutrient resources, liver function, gastrointestinal (GI) capacity, and environmental cues, such as smell and sight, all of which are processed by the brain (15). Recently, considerable attention has been directed to the role of various cytokines as mediators of the anorexia-cachexia syndrome, particularly tumor necrosis factor (TNF). Cytokines are discussed in detail later in this chapter under mediators of cancer cachexia.

NUTRITIONAL EFFECTS OF CANCER TREATMENTS

Radiation

The site, magnitude, and duration of radiation therapy all influence the severity of nutritional injury. This injury may be associated with both acute and late effects of radiation therapy (16,17,18 and 19).

After radiotherapy of the oral cavity and pharynx, patients can experience both heightened and suppressed taste sensation. Loss of taste is severe and rapid after oropharyngeal irradiation, as measured by quantitative tests of sensitivity to sour, sweet, and bitter substances. Fortunately patients often regain preirradiation taste sensitivity 60–120 days after therapy is completed.

Radiation to the head and neck may inhibit adequate salivation, leading to changes in eating habits. Also, patients may experience increased sensitivity of their teeth to extreme temperature and sweetness. In a study of weight loss during a 6- to 8-week course of external beam radiation therapy to the head and neck regions, 93% of 114 patients lost an average of 3.7 kg. In addition, approximately 9% of individuals lost more than one-tenth of their body weight during their 6- to 8-week course of radiation (17).

Radiation to the gastric area and small and large intestine is associated with various complications that may influence nutritional status. Low doses of gastric irradiation reduce gastric acidity whereas higher doses may induce ulcer formation. Nausea, vomiting, and diarrhea are common in individuals undergoing radiation to the small and large bowel. In addition, chronic diarrhea or bowel obstruction may develop due to radiation-induced enteritis following high-dose GI irradiation.

Upper abdominal radiation may produce radiationinduced hepatitis, characterized by anorexia, nausea, vomiting, and abdominal distention. This disorder is usually temporary. Radiation to the pancreas may similarly result in acute anorexia, nausea, and vomiting.

Chemotherapy

Chemotherapy can affect host tissue in addition to the targeted neoplasm and thus cause short-term nutritional defects. Almost every major class of compound used in chemotherapy and immunotherapy products can produce nausea and vomiting (20) accompanied by anorexia. This often results in reduced dietary intake, electrolyte imbalance, weakness, and progressive weight loss (21).

Mucosal toxicity, manifested as oral ulcerations, cheilosis, glossitis, and pharyngitis, may be inevitable with the use of some chemotherapeutic agents. This often leads to odynophagia and anorexia. Specific agents, such as actinomycin D, cytarabine, 5-fluorouracil, hydroxyurea, and methotrexate, can produce ulcerations of the entire GI epithelium (22,23). Therapy itself does not induce malabsorption but, because of its side effects, can aggravate the effect of tumor-related malabsorption syndromes (22). Small intestinal absorptive function with either a single agent or combination chemotherapy remains well preserved in most instances. Nutrition support is usually unnecessary in the initially well-nourished patient if the ill effects of chemotherapy are significantly limited in time and intensity.

Many major organ systems are affected by chemotherapeutic agents, resulting in decreased efficiency of metabolism. The liver is especially vulnerable, and hepatic injury is commonly associated with anorexia. Diffuse hepatocellular damage often results in hypoalbuminemia. Several agents affect other organ systems. Hydroxyurea may cause renal impairment. Doxorubicin may cause cardiac toxicity leading to congestive heart failure, water retention, and electrolyte imbalance. Ohnuma and Holland (20) and Carter (24) provide extensive discussions of the nutritional consequences of chemotherapy and immunotherapy.

Surgery

Nutritional depletion can be attributed to surgical intervention in many cancer patients. Nutrition support can be a beneficial tool, as a patient with good nutritional status develops fewer postoperative complications. If nutritional assessment reveals protein calorie malnutrition, elective surgery can even be delayed until nutritional status improves (25). Yamada et al. (26) analyzed the association between nutritional parameters and postoperative complications in 440 patients with gastric cancer. The frequency of postoperative complications was highest in patients with stage IV gastric cancer. A strong interrelationship was found between nutritional status and postoperative complications.

Certain surgical procedures require nutritional intervention. Radical resection of the oropharyngeal area often necessitates postoperative tube feeding (27). Conditions associated with esophagectomy and esophageal reconstruction may include delayed gastric emptying secondary to vagotomy, malabsorption, and the development of a fistula or stenosis. Gastric surgery may result in dumping syndrome, malabsorption, and/or hypoglycemia.

The site and extent of intestinal resection can result in a variety of nutritional complications. Jejunal resection can decrease the efficiency of absorption of many nutrients. Ileum resection commonly results in vitamin B_{12} deficiency and bile salt losses. With extensive small bowel resection, malabsorption leading to malnutrition is common, as reported in jejunoileal bypass (28). Abnormalities in sodium and water balance are commonly associated with ileostomy and colostomy formation. In addition, gastric and intestinal bypass surgery to relieve obstruction can result in a blind loop syndrome with specific nutritional deficiencies.

Individuals with pancreatic cancer should be nutritionally assessed because they frequently lose weight before their diagnosis and surgical intervention. After pancreatectomy, malabsorption and endocrine as well as exocrine insufficiency are common problems that may require insulin and pancreatic enzyme replacement. Cancer patients undergoing ureterosigmoidostomy may experience hyperchloremic acidosis and hypokalemia in addition to other more common postoperative problems.

If it is anticipated that nutritional intervention will be required postoperatively, a nasoenteric feeding tube can be placed intraoperatively. With patients in whom a longer recuperative course is anticipated, placement of a gastrostomy tube or jejunostomy tube may be more appropriate.

Energy Metabolism in the Cancer Patient

Altered metabolism of nutrients is common in cancer anorexia. A wasting of 100 nonprotein calories per day in futile pathways can contribute to major losses in both total weight and lean body mass over the long term. Abnormalities in carbohydrate, protein, and lipid metabolism are common. The inability of cachectic cancer patients to gain lean body mass despite adequate nutrition support is likely due to the effect of the tumor on host metabolism. The Pancreatic Cancer Task Force reported that 80% of 924 patients with pancreatic cancer had weight loss before diagnosis (29). Whereas 50% of the pancreatic cancer patients studied had experienced weight loss longer than 2 months before diagnosis, only 26% of these patients reported anorexia during this period.

Carbohydrate Metabolism

Abnormal glucose metabolism, a major source of caloric wasting, is a hallmark of cancer cachexia (30). Both increased glucose production and utilization as well as insulin resistance are characteristic. Glucose intolerance may be attributable to a reduced tissue sensitivity to insulin (31). There may be decreased pancreatic b-cell receptor sensitivity in cancer patients as well, leading to inadequate insulin release in response to a glucose load. Such abnormalities in peripheral glucose metabolism

simulate a type II diabetic state but also share elements similar to the stress state (32,33,34,35 and 36).

An increase in gluconeogenesis in the liver of the cancer patient is a common finding. This can be the result of an increased release of glucogenic fuel substrates, such as lactate and alanine (34,36), as well as an increased induction of hepatic gluconeogenetic enzymes (33). The energy drain created by increased hepatic gluconeogenesis leads to host depletion of protein and calories. Elevation of hepatic glucose production in a tumor-bearing host requires energy; three moles of adenosine triphosphate is necessary to convert each mole of lactate to glucose. Therefore, abnormal glucose kinetics can result in calorie-consuming futile metabolic cycles, with a drain on host energy. Cancer patients who lose weight may exhibit increases in glucose flux and glucose oxidation rates. This mechanism is central in the development of host depletion in cachexia, although the energy expenditure involved in these processes suggests that they are more likely associative than causative (37,38).

Protein Metabolism

Cancer anorexia is accompanied by wasting of host protein mass, leading to fatigue, weakness, and altered host cellmediated immune response. Clinical signs include skeletal muscle and visceral organ atrophy, hypoalbuminemia, and anergy. Host protein wasting results from alterations in total body protein turnover, muscle protein synthesis and catabolism, hepatic protein metabolism, and plasma secretory protein levels. Several studies have shown that cachectic cancer patients have elevated rates of protein turnover and that the normal adaptation of reduced protein metabolism (i.e., protein sparing) in the setting of starvation does not occur (39). With nutritional depletion, patients with cancer anorexia continue to manifest elevated rates of skeletal protein mobilization rather than the normal response of decreased protein turnover and protein sparing. Protein turnover rates in cachectic cancer patients are significantly higher compared with similarly malnourished control patients without cancer. A loss of less than 100 g of protein nitrogen or 625 g of body protein equal to 2.5 kg of lean body mass can produce mild protein malnutrition, fatigue, weakness, and altered immune response (40). Explanations for this phenomenon of increased nitrogen turnover remain controversial. However, the findings suggest an injury response to cancer with the tumor acting as a “nitrogen sink.”

Lipid Metabolism

The most common impairments in lipid metabolism seen in cancer patients are hyperlipidemia and depletion of fat stores (41,42 and 43). Abnormal lipoprotein lipase activity alters the ability of fatty acids to be utilized as protein-sparing energy fuels and is a major cause of protein malnutrition. The hyperlipidemia seen in cancer patients is significant and may play a role in disease outcome. Elevated lipid levels may have an inhibitory effect on monocytes and macrophages. The combination of increased lipolysis, fatty acid recycling via very low density lipoprotein, and the impairment of lipoprotein lipase enzyme activity leading to decreased lipid clearance can be immunosuppressive.

Suppression of lipoprotein lipase occurs in cancer patients, but the mechanism is different from that which occurs in starvation. In the latter, lipid mobilization occurs despite a decrease in lipoprotein lipase activity because of a 50% decrease in plasma insulin levels. Vlassara et al. (44) have shown that cancer-associated reductions in plasma lipoprotein lipase are accompanied by normal or even increased insulin levels. This represents a maladaptive host response, since insulin promotes lipid storage, not fat oxidation. Impaired glucose and fat oxidation provide a sink for loss of gluconeogenic amino acids, thus producing an energy deficit and malnutrition.

Biochemical Mediators of the Anorexia-Cachexia Syndrome

The anorexia-cachexia syndrome incorporates a group of symptoms and signs such as inanition, anorexia, weakness, tissue wasting, and organ dysfunction (2,14,45,46 and 47). Potential etiologies of cancer anorexia are listed in Table 68-2. Cachexia was previously thought to be the result of increased energy demanded by the growing tumor mass. Recent research has demonstrated that it is primarily due to major metabolic abnormalities, such as profound lipolysis and loss of skeletal and visceral proteins, both of which are caused by immune mediators (e.g., TNF and interleukin-6), and tumor byproducts (e.g., lipolytic hormone). This means that anorexia, an almost universal characteristic of cachexia, should be interpreted as the result of metabolic abnormalities rather than the main cause of cachexia (48).

There has been much interest in the possible role of cytokines in cancer anorexia. Prominent cytokines include TNF, interleukin-1a and b (IL-1), interleukin-6 (IL-6), interferon-a (IFN-a), and differentiation factor, also known as leukemia inhibitory factor (49). The peptides are pyrogens, and their administration, with the exception of IL-6, can produce many of the systemic vascular effects seen in sepsis and shock. For example, IL-1 and TNF-a share the capacity to up-regulate gene transcription of endothelial cell adhesion molecules, increase procoagulant activity, promote the transendothelial migration of leukocytes out of the vascular component into the pulmonary epithelium, and activate the release of toxic superoxide and other enzyme products from neutrophils (50).

Cachexia-anorexia syndrome is characterized by progressive weight loss, lipolysis, loss of visceral and skeletal protein mass and profound anorexia (51). Cachexia is characterized by dramatic loss of triglycerides from adipose tissue and proteins from skeletal muscles (52). Weight loss decreases a patient's chance of survival, and patients with cachexia experience more complications after surgery, radiation therapy, and chemotherapy. In addition, cachexia reinforces the weakness associated with anorexia and chronic nausea and is a source of psychological distress for patients and their families.

Features of cancer cachexia can be reproduced by cytokine administration. For example, IL-1 (53) and, to a lesser extent, TNF-a (54) and IFN-a (55) are potent anorexia-producing agents. Some cytokine effects are mediated through the hypothalamus (56), and others act directly on the GI tract, causing decreased gastric emptying (54). Other cytokines may promote cachexia by increasing resting energy expenditure. Warren et al. (57) reported that cancer patients receiving cytokines as antineoplastic therapy had a dose-dependent increase in resting energy expenditure.

A mechanism proposed by Kern and Norton (2) to explain the anorexia and metabolic derangements of the anorexia-cachexia syndrome is shown in Figure 68-1. Some cancers incite a paracrine-induced systemic host response with production of cytokines such as interleukins or cachectin/TNF. These are secreted by immune cells and may be part of the host defense in an attempt to destroy the tumor. However, cytokines have negative secondary effects on host organs, resulting in anorexia and abnormalities in carbohydrate, protein, and lipid metabolism. Mobilization of nutrients from fat and skeletal muscle during the acute phase of sepsis or in trauma patients rapidly provides a physiological source of nutrients to the liver so that it can synthesize acute injury proteins. In the cancer patient, the low-grade release of cytokines persists because of the metabolic activity of the tumor and eventually causes severe depletion of host cell mass. The anorexia of chemotherapy, radiotherapy, or surgery only exacerbates this process, adding to the net effect of host depletion. The “at-risk” cancer patient can be identified by a rapid weight loss of greater than 10% of usual body weight.

FIGURE 68-1. Proposed mechanism of the cancer anorexia syndrome. Tumor–host interaction results in production of metabolically active cytokines that cause anorexia and abnormalities in host intermediary metabolism. FFA, free fatty acids. (From Kern KA, Norton JA. Cancer cachexia. JPEN J Parenter Enteral Nutr 1988;12:286–298, with permission.)

Cancer cachexia is a syndrome of progressive wasting which also has been suggested to be mediated by TNF-a, IL-1, IL-6, IFN-g, and leukemia-inhibitory factor (58,59). Recently a novel, tumor-derived cachectic factor was identified in the murine MAC16 colonic adenocarcinoma model of anorexia. This factor, provisionally named proteolysisinducing factor, was subsequently identified in the urine of weight-losing patients with cancer but not in the urine of weight-stable patients with cancer or weight-losing controls with benign disease (58,60).

Fordy et al. reported that patients with significant weight loss from colorectal liver metastases required a large tumor volume (61). This weight loss was not explained by changes in diet, quality of life, or hormones, but activation of the innate immune systems and incomplete activation of the acquired immune systems were likely to be involved. Agents that attenuate either the acute-phase inflammatory response or T lymphocyte IL-2 receptor up-regulation might reduce weight loss in patients with

metastatic disease (61).

Preventing malnutrition is easier than reversing it. Reversing malnutrition in a patient with advanced cancer is nearly impossible. Patients with cancer often lose weight and become malnourished at a time when they most need nutrition support (62). Current pharmacological therapies as well as complementary and alternative methods may be recommended for patients with cancer cachexia (63). In recent years, medications such as corticosteroids and progestational drugs, have proven effective in relieving symptoms of cancer cachexia. Corticosteroids have a limited effect (lasting up to 4 weeks) on symptoms such as appetite, food intake, sense of well-being and performance status, but none of the studies proved that patients had weight gain (48). Recent studies involving terminally ill patients have shown that progestational drugs improved the symptoms of fatigue and anorexia even in the absence of weight gain. If abruptly discontinued, both megestrol and medroxyprogesterone could induce thromboembolic phenomena, breakthrough vaginal bleeding, peripheral edema, hyperglycemia, hypertension, Cushing's syndrome, alopecia, adrenal suppression, and adrenal insufficiency. However, in most clinical trials, the adverse effects rarely led patients to discontinue these drugs (64).

ADJUNCTIVE NUTRITION SUPPORT DURING ANTINEOPLASTIC TREATMENT

The goal of nutritional care in the cancer patient should always be considered supportive whether the aim of primary therapy is cure or palliation. Nutritional therapy should be aimed at improving metabolic status, body composition, functional status, and, ultimately, quality of life. Nutrition support can prevent further deterioration in all of these parameters. However, because of the metabolic derangements of cancer cachexia, attempts to reverse severe nutritional depletion are almost universally unsuccessful.

Concerns also exist over the risk of disproportionately stimulating tumor growth as well as the ability to replete the malnourished cancer patient (65). Animal studies have been inconclusive concerning this issue. Undoubtedly in a cachectic noncancer patient receiving either total parenteral nutrition (TPN) or enteral feeding, nitrogen balance, wound healing, and outcome are improved. However, controversy continues about the role of nutrition support in cancer patients. The use of nonvolitional feeding, particularly intestinal feeding tubes and TPN, is designed to prevent the nutrition-related complications of cancer therapy (5). In the setting of chemotherapy, the risk of providing nutrition support inappropriately must be foremost in clinical decision making. TPN is not indicated for patients with advanced metastatic cancer who are not receiving antineoplastic treatment, and the routine use of TPN in cancer patients who can tolerate enteral nutrition is unjustified. The potential adverse consequences of nutrition support in the setting of cancer make it important to establish the therapeutic benefits before the initiation.

“If the gut works, use it” has become the motto of most nutrition support teams around the country. The use of the GI tract is encouraged whenever possible because it is safe, physiological, and cost effective. There is also evidence that enteral nutrition may improve visceral protein synthesis. In addition, enteral feeding is superior to TPN in supporting GI mucosal growth and function. This may be important for critically ill patients in whom the gut mucosal barrier may become compromised.

Nutrition Support in the Perioperative Setting

Prospective randomized clinical trials evaluating the clinical efficacy of nutrition support in cancer patients undergoing surgical therapy were recently reviewed (66). Twenty-seven trials were identified evaluating TPN in cancer patients who underwent surgery (67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93 and 94). Only five trials found statistically significant differences in clinical outcomes (69,74,78,79,86). One study reported fewer postoperative complications and decreased mortality in patients with GI carcinoma receiving preoperative TPN (74). Two other trials (69,79) reported decreased postoperative complications in patients receiving preoperative TPN. However, a large multicenter Veterans Affairs cooperative study (86) found similar rates of complications in the TPN and control groups. In addition, the study observed a statistically significant increase in the infection rate in patients receiving preoperative TPN and concluded that routine use of TPN in the perioperative setting is not indicated. Seven trials evaluated hospital length of stay (69,78,82,84,85,87,94), and only one (78) reported a significantly shorter length of stay in patients given TPN perioperatively. There were two meta-analytic reviews of prospective and mixed clinical trials published recently (95,96). Both reviews found that the combined rate of complications or mortality in patients receiving perioperative TPN was one-half to two-thirds that of the control group. Klein and Koretz et al. (66) report that data from studies providing at least 7 days of preoperative TPN suggest that the rate of preoperative complications can be decreased by approximately 5%, but that this result may not be justified economically.

Seven trials (92,97,98,99,100,101 and 102) investigated the use of enteral nutrition in surgical patients with cancer. Perioperative mortality and length of hospital stay were similar in both enterally fed and control patients. A study looking at the effect of postoperative jejunostomy tube feeding with a formula enriched with arginine, ribonucleic acids, and omega-3 fatty acids in cancer patients reported fewer complications and shortened length of stay compared with patients receiving a standard formula (103).

Nutrition Support in Patients Treated with Chemotherapy

In recent studies evaluating the use of TPN in patients undergoing chemotherapy (104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127 and 128), there was no advantage in overall survival in those receiving nutrition support. Only one trial in patients with squamous cell lung cancer reported an increase in survival of patients given TPN (125). Other trials in patients with colorectal cancer (98) and adenocarcinoma of the lung (128) reported decreased survival in the TPN-treated groups. Two meta-analytic reviews (95,129) concluded that TPN provided no added benefits in terms of survival, tumor response, or chemotherapy toxicity. However, TPN did seem to increase the infection rate.

Studies evaluating enteral nutrition in patients receiving chemotherapy were difficult to evaluate due to differences in composition, timing, and duration of nutritional therapy (66). However, no therapeutic benefit was reported in these trials in terms of survival, tumor response, or chemotherapy toxicity (130,131,132,133,134 and 135).

Nutrition Support in Patients Treated with Radiation Therapy

Four prospective and mixed controlled trials evaluated the effect of TPN in patients undergoing radiation therapy for cancer, with no difference in survival reported between TPN and control subjects (136,137,138,139 and 140). Moreover, the rate of infection was greater in patients receiving TPN than in controls in one study reporting infection rates (139).

Seven trials reported the outcome of enteral nutrition in patients receiving radiation (141,142,143,144,145,146,147 and 148). There was no difference in survival noted in the two studies that reported survival rates. Side effects were fewer in nutritionally treated patients receiving radiation for abdominal and pelvic cancer (142,143 and 144) but were greater in one study looking at head and neck cancer patients (146).

Nutrition Support in Patients Treated with Bone Marrow Transplantation

Two studies investigated the use of nutrition support in patients treated with bone marrow transplantation (BMT). BMT requires intensive chemotherapy and often radiation, leading to esophagitis and enteritis, resulting in severe nutritional depletion. In one study, Weisdorf et al. (149) reported increased survival in patients who received TPN as compared with controls. In a study by Szeluga et al. (150), patients received either TPN or enteral nutrition post-BMT, and survival did not differ between the two groups. However, the infection rate was higher in patients receiving TPN as compared with those given enteral therapy.

Several studies have evaluated the efficacy of glutamineenriched TPN in patients undergoing BMT. Glutamine is an important intestinal fuel that attenuates mucosal damage, thereby potentially decreasing bacterial translocation and bacteremia. Glutamine-enriched TPN is hypothesized to decrease the occurrence of systemic infection in those patients who are predisposed. In one study (151), Ziegler et al. reported similar survival but decreased infection rates and shortened length of stay in patients receiving glutamine-TPN versus thoose receiving standard TPN. However, Schloerb et al. (152) reported similar rates of survival, infections, and length of hospitalization when involving patients with both hematological and solid tumors.

In conclusion, most clinical trials have failed to demonstrate the clinical efficacy of providing nutrition support to most patients with cancer. However, nutrition support during treatment for cancer should not be denied in patients judged to have life-threatening malnutrition, as is provided for patients with benign disease (153).

GUIDELINES AND RISK FACTOR ASSESSMENT FOR NUTRITION SUPPORT

Global Assessment Tools

The implementation of nutrition support teams as well as proper guidelines and protocols for surveillance are the first steps in ensuring that malnourished patients are identified through nutritional screening (Table 68-3). Three simple assessment measures discussed below can be used initially to screen for protein calorie malnutrition: height and weight to determine body mass index (BMI) (154), percent of regular weight lost, and serum albumin levels. These measures are sensitive enough to identify most patients with protein calorie malnutrition. Other indicators from the Nutrition Screening Initiative level II screen (155) include midarm muscle

circumference, triceps skinfold, and serum cholesterol. In addition, clinical history, drug use, eating habits, living environment and income, and functional status, as well as mental and cognitive functioning, need to be assessed.

	Standards
Initial evaluation	
Body mass index (kg/m²)	(see Table 68-5)
Rate weight loss (% weight loss/time)	(see Table 68-6)
Serum albumin (g/dl)	≥3.5 g/dl
Comprehensive evaluation	
Anthropometrics	
Triceps skinfold (mm)	(see Table 68-8)
Arm muscle circumference	(see Table 68-8)
Biochemical indices	
Urine	
Creatine height index	
Urine urea nitrogen	6–7 g/24 h
Nitrogen balance	0–1 g/24 h
Catabolic index	(see text)
Serum	
Transferrin (g/dl)	≥170 g/dl
Total lymphocyte count	≥1500 cells/mm³
Prealbumin	18–45 mg/dl
Immune function: delayed hypersensitivity	
Skin tests	
Candida	≥5 mm induration
Mumps	≥5 mm erythema/induration
Tetanus toxoid	≥5 mm induration

TABLE 68-3. NUTRITIONAL ASSESSMENT PARAMETERS

Other indicators are also available (156,157,158,159 and 160). Buzby et al. (156) developed a Prognostic Nutritional Index (PNI) evaluating serum albumin, serum transferrin, triceps skinfold, and delayed hypersensitivity as a multiparameter index of nutritional status for preoperative nutrition support.

The PNI is defined as

$$PNI\ (\%) = 158 - 16.6(Alb) - 0.78(TSF) - 0.20(TFN) - 5.8(DH)$$

where *Alb* is serum albumin in g/100 ml, *TSF* is triceps skinfold in mm, *TFN* is serum transferrin in mg/100 ml, and *DH* is cutaneous delayed-type hypersensitivity reactivity to any three recall antigens and is scored as 0 (nonreactive), 1 (<5 mm induration), or 2 (>5 mm induration) (19). A PNI of less than 40% is categorized as low risk, 40–49% intermediate risk, and greater than 50% high risk.

Another index, the Nutritional Risk Index, was developed by the Veterans Affair TPN Cooperative Study Group (11). This index approximates the degree of malnutrition based on a specific constant, serum albumin levels, and percent weight loss.

Perhaps the most beneficial tool for nutritional screening in the oncology patient is the Subjective Global Assessment (SGA) (Table 68-4) modified by Ottery (161,162) for the practicing oncologist and other health care providers. The original SGA (163) estimates nutritional status on the basis of medical history (i.e., weight and weight history, dietary intake, GI symptoms with >2 weeks duration, functional status, and metabolic demands) and physical examination (five determinations of muscle, fat, and fluid status) (164). On the basis of these features, the patient is categorized as (a) well nourished, (b) having moderate or suspected malnutrition, or (c) having severe malnutrition (165). Two modifications of the SGA have been developed specifically for use in oncology patients (161,162). Figure 68-2 demonstrates an algorithm for optimal nutritional oncology intervention based on the SGA (166).

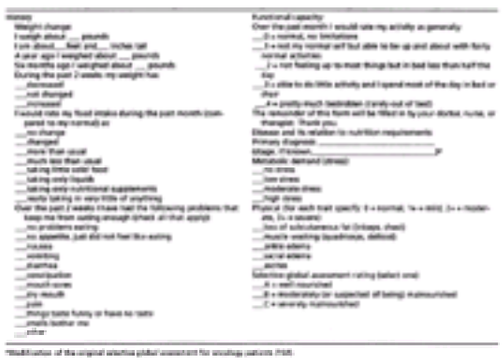


TABLE 68-4. PATIENT-GENERATED SUBJECTIVE GLOBAL ASSESSMENT OF NUTRITIONAL STATUS

FIGURE 68-2. Algorithm of optimal nutritional oncology intervention: baseline nutritional status (SGA). “Risk” refers to nutritional risk. GI, gastrointestinal; SGA, subjective global assessment; SGA-A, well nourished; SGA-B, moderately malnourished; SGA-C, severely malnourished. (From Kern KA, Norton JA. Cancer cachexia. JPEN J Parenter Enteral Nutr 1988;12:286–298, with permission.)

Individual Screening Tools

Body Mass Index

The BMI (144) may be a useful tool to identify individuals at risk for protein calorie malnutrition (Table 68-5).

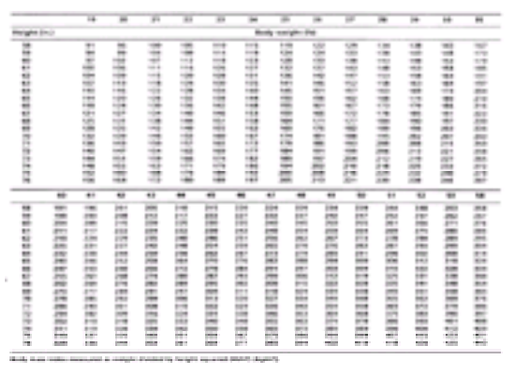


TABLE 68-5. BODY MASS INDEX TABLE

$$BMI = \text{weight (kg)}/\text{height (m}^2\text{)}$$

A BMI of less than 22 may be indicative of possible protein calorie malnutrition, especially among cancer patients.

Weight Loss

Documentation of the patient's weight history is an important and easily obtainable index for the suspected presence or progression of malignancy. There are several parameters available to interpret weight measurements including the weight/height index and the percentage of weight lost. Because the patient's height remains essentially constant, the weight/height index remains a reliable tool for estimating nutritional status. An index less than 90% of standard would suggest moderate nutritional risk whereas a weight/height index less than 75% of standard suggests severe malnutrition.

Table 68-6 focuses on the percentage of regular weight lost. This too can be a good indication of the severity of nutritional deficiency. For example, “severe” weight loss should be considered with a 5% loss of body weight in 1 month or a 10% loss within 6 months (167).

	Significant weight loss (%)	Severe weight loss (%)
1 wk	1–2[a]	>2
1 mo	5	>5
3 mo	7.5	>7.5
6 mo	10	>10

[a]Percent weight change, usual weight – actual weight divided by 100 x usual weight.
From Blackburn GL, Harvey KB. Nutritional assessment as a routine in clinical medicine. *Postgrad Med* 1982;71:46, with permission.

TABLE 68-6. EVALUATION OF WEIGHT CHANGE

Fluid balance or degree of hydration also affects the accuracy of the change in weight. Fluid retention or loss can account for significant weight shifts rather than changes in body cell mass or protein content. Therefore, fluid balance should be closely monitored.

Serum Albumin

Serum albumin concentration is a commonly used index of nutritional status. Albumin, synthesized in the liver, has a half-life of approximately 20 days with normal serum concentrations of greater than 3.5 g/dl (Table 68-3).

As a nutritional marker, serum albumin concentrations may be beneficial for detecting malnutrition. Table 68-7 demonstrates that, in hospitalized patients, hypoalbuminemia is associated not only with anergic immune status but with increased morbidity and mortality, and is a poor prognostic indicator (168).

	<10%	<25%	50%	>75%	>90%
Anergy	5.2	4.2	3.2	2.2	1.2
Sepsis	4.3	3.7	3.1	2.5	1.9
Death	4.9	4.0	3.2	2.3	1.5

From Langstein HN, Norton JA. Mechanisms of cancer cachexia. *Hematol Oncol Clin North Am* 1991;5:103–123, with permission.

TABLE 68-7. PROBABILITY ESTIMATES USING SERUM ALBUMIN

There are, however, limitations to the use of serum albumin concentration as a nutritional index for stressed and critically ill patients. During an acute illness or stress, such as injury, infection, or surgery, serum albumin synthesis decreases and hypoalbuminemia ensues. In addition, due to the long halflife, serum albumin does not respond on a daily or weekly basis to nutrition support. Finally, serum albumin concentrations can be affected by fluid status and volume repletion.

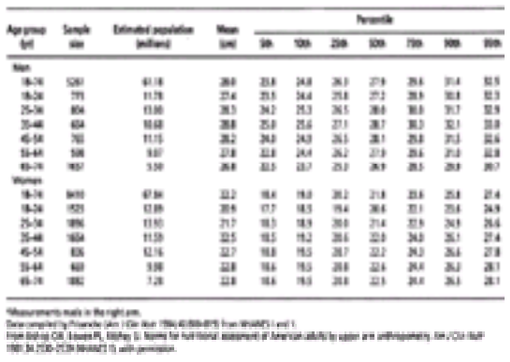
Anthropometrics

Anthropometric techniques are tools that may be beneficial in defining fat stores in the patient with cancer. One of the major sites of fat deposition in the human body is the subcutaneous space (19). Subcutaneous fat represents approximately 30% and 33% of total body fat in men and women, respectively; these numbers vary according to age, level of obesity, and measurement techniques (12).

A useful anthropometric assessment of body fat mass is the triceps skinfold measurement (TSF). This is performed by using large calipers at the upper left arm. Knowing the TSF, one can derive the more valuable arm muscle circumference (AMC):

$$AMC = \text{arm circumference} - TSF$$

The AMC is compared with standard tables (Table 68-8), and values less than 60% of standard are consistent with protein depletion (19). As with all anthropometric techniques, interobserver and intraobserver variation ranges from 15% to 20%, and the exact correlation between upper arm circumference and total body protein stores is unknown.



Age group (yr)	Sample size	Estimated population (millions)	Mean (cm)	Percentile						
				5th	10th	25th	50th	75th	90th	95th
Men										
18–74	5261	61.18	28.0	23.8	24.8	26.3	27.9	29.6	31.4	32.5
18–24	771	11.78	27.4	23.5	24.4	25.8	27.2	28.9	30.8	32.3
25–34	856	13.66	28.3	24.2	25.3	26.5	28.0	30.0	31.7	32.9
35–44	654	10.68	28.8	25.0	25.6	27.1	28.7	30.2	32.1	33.0
45–54	702	11.15	28.2	24.0	24.8	26.5	28.1	29.8	31.3	32.6
55–64	598	9.87	27.8	22.8	24.4	26.2	27.9	29.6	31.0	32.0
65–74	957	5.59	26.8	22.5	23.7	25.0	26.9	28.5	29.9	30.7
Women										
18–74	6410	67.84	22.2	18.4	19.0	20.2	21.8	23.6	25.8	27.4
18–24	1025	13.89	20.9	17.7	18.3	19.4	20.8	22.1	23.6	24.9
25–34	1096	13.93	21.7	18.3	18.9	20.0	21.4	22.9	24.9	26.6
35–44	1054	11.59	22.5	18.5	19.2	20.6	22.0	24.0	25.1	27.4
45–54	826	9.16	22.7	18.8	19.5	20.7	22.2	24.2	26.6	27.8
55–64	663	5.98	22.8	18.6	19.5	20.8	22.6	24.4	26.2	28.1
65–74	886	7.28	22.8	18.6	19.5	20.8	22.5	24.4	26.3	28.1

[a]Measurements made in the right arm.
Data compiled by Pichardo (Am J Clin Nutr 1988;48:1556–1577) from NHANES I and I.
From Bishop CW, Edwards PR, Ridley JL. Norms for nutritional assessment of American adults by upper arm anthropometry. Am J Clin Nutr 1991;54:2135–2139 (NHANES II) with permission.

TABLE 68-8. MIDARM MUSCLE CIRCUMFERENCE IN ADULTS (18–74 YEARS), UNITED STATES[a]

Transferrin

Transferrin is a 90-kd globulin that binds and transports iron. The half-life of transferrin, which is primarily synthesized in the liver, is 8–10 days. Visceral protein depletion is reflected with transferrin levels less than 170 g/dl. This makes it more sensitive than albumin as an index of improvement in nutritional status. There are, however, two instances when transferrin levels are unreliable for nutritional status: in iron-deficient or iron-overloaded patients who tend to show high and low transferrin levels, respectively, and in patients who have had multiple transfusions (7).

Delayed Hypersensitivity

Assessment of the function of the cellular immune system through delayed hypersensitivity testing to common skin antigens can be a marker of nutritional status. Anergy has been correlated with an increased incidence of postoperative morbidity and mortality (169). The common recall antigens used are *Candida*, mumps, dermatophytes, or tetanus toxoid. After 24–48 hours, 5 mm or greater of induration is considered a positive response. Cellular immunity is most sensitive to malnutrition, but protein deficiency also reflects leukocyte function, particularly immune cell activation and cytokine release.

Evaluation of Ongoing Nutrition Support

Patients undergoing administration of nutrition support require assessment of several parameters to tailor daily requirements of specific nutrients. Many of these parameters, notably serum albumin, AMC, and BMI, are not sensitive enough to detect the short-term effects of nutrition support. In addition to daily electrolyte determinations, physical examination, and accurate body weights, other parameters, such as nitrogen balance, may be more beneficial in assessing the impact of nutritional therapy on a short-term basis.

Health care providers must, however, differentiate an increase in weight caused by fluid retention from lean body mass. Malnourished patients who are suddenly overfed can develop an increase in intravascular volume, congestive heart failure, and electrolyte abnormalities, which can be fatal (170).

Nitrogen Balance

The nitrogen balance determination is a dependable measure that can reflect the influence of nutrition support on lean body mass. Nitrogen balance reflects the difference between nitrogen intake versus output over a 24-hour period. With 1 g of nitrogen representing 6.25 g of protein, the nitrogen balance is calculated as

$$\text{Nitrogen balance} = \text{protein intake (g)} \div 6.25 - (\text{24-hour urine urea nitrogen} + 4\ \text{g})$$

The principal form of urine nitrogen is called *urine urea nitrogen*, which can be easily measured. Urea excreted in the urine reflects protein degradation. In addition to urea, other forms of nitrogen are excreted, including nonurea urine nitrogen, fecal nitrogen, and integumental nitrogen. These are lost at a fairly constant rate except when diarrhea is present. In calculating nitrogen loss, 4 g is added to the nitrogen output as an estimate of fecal and integumental losses.

NUTRITION SUPPORT

Parenteral Nutritional Requirements

Caloric Requirements

The “gold standard” for estimating basal energy requirements was derived by Harris and Benedict around the turn of the century (171). Basal metabolic requirements (BMRs) can be calculated using the following Harris-Benedict equations:

$$\text{BMR for males} = 66.4730 + (13.7516W) + (5.0033H) - (6.7550A)$$

$$\text{BMR for females} = 65.5095 + (9.563W) + (1.8496H) - (4.6756A)$$

where W is weight in kilograms, H is height in centimeters, and A is age in years.

The primary goal of parenteral and enteral nutrition support is to supply adequate protein and nonprotein calories to prevent further catabolism and promote the accrual of protein. The use of parenteral nutrition, although controversial in some settings, has been accepted as an effective means of sustaining life and promoting recovery in critically ill patients incapable of ingesting, absorbing, or assimilating nutrients. TPN has also proved appropriate for similar noncritically ill patients who have preexisting malnutrition and for nonstressed but hospitalized patients who can take nothing by mouth for 5 to 7 days. These goals of parenteral nutrition remain supportive: (a) improving wound healing, (b) bolstering immune function, (c) influencing acid-base and mineral homeostasis, and (d) minimizing obligate nitrogen loss in the catabolic postinjury state. These goals are achieved by (a) providing substrate (protein, carbohydrate, lipid, electrolytes, minerals, and vitamins) for ongoing metabolic functions, (b) improving cardiac and respiratory function by restoring glycogen stores in cardiac and diaphragmatic muscle, and (c) potentially modifying the systemic inflammatory response (167,170,172).

All critically ill patients require a thorough nutritional assessment to determine who is likely to benefit from nutrition support and whether nutrition is to be provided via an enteral route, parenteral route, or a combination. Three principal factors predict the need for nutrition support: current nutritional status (i.e., body composition) and recent weight loss, the anticipated duration of inadequate nutrient intake, and the presence and degree of the stress response. A nutritional assessment begins with a thorough history and physical examination. The BMI is often a useful indicator. Defined as weight in kilograms divided by the square of height in meters, it normalizes body weight for height and is independent of sex. A value less than 18 is consistent with significant malnutrition. Weight alone may be a poor indicator of nutritional status, as short-term fluctuations in total body water may account for changes in weight. Temporal and peripheral muscle wasting may occur, signifying probable malnutrition even in the face of weight gain. Upper arm anthropometry is a useful tool for assessing malnutrition. A value below the fifth percentile is consistent with a loss of approximately 30% of normal lean body mass and is an absolute indication for nutritional intervention. Serum levels of visceral protein markers such as albumin, prealbumin, retinol-binding protein, and transferrin, have commonly been used as indicators of nutritional status (167,170).

Choosing the appropriate route of nutrition support for a critically ill patient is an important decision predicated on the patient's clinical situation. Although enteral feeding is always the preferred route for patients with a functional GI tract, many patients have relative or absolute contraindications to enteral feedings. Patients with severe diarrhea, abdominal distention, high nasogastric tube output, pancreatitis, or unobtainable safe access to the GI tract are poor candidates for enteral nutrition. The complications of enteral nutrition include pulmonary aspiration, diarrhea, and intestinal ischemia or infection. Owing to the seriousness of intestinal ischemia, hemodynamically unstable patients with low cardiac outputs and patients on moderate to large doses of alpha agonists should not be fed by the enteral route. In addition, many patients are difficult to feed safely enterally, because of either feeding intolerance or respiratory failure with aspiration risk.

The mild to moderately stressed patient usually requires 25–35 kcal/kg and 1.5 g of protein/kg of ideal body weight in order to maintain positive nitrogen balance.

Nonprotein calories are supplied by both carbohydrates and lipids, with glucose being the major energy source for the central nervous system, red blood cells, and renal medulla. These organ systems require a minimum of 100–150 g/day (19). The maximal infusion of dextrose given should be 5 mg/kg/minute. Exceeding this rate may lead to hepatic steatosis and excess fat synthesis and carbon dioxide production (19). The caloric density of glucose is 3.4 kcal/g; approximately 60–70% of nonprotein calories should be provided as dextrose (172).

Lipid Requirements

Fat emulsions, derived from soybean or safflower oil, provide 2.0 kcal/ml in standard 20% solutions. The usual dose of lipid is 0.5–1.0 g/kg/day, with the maximum of 2.5 g/ kg/day (173). Lipid emulsions are usually formulated to provide approximately 30% of total nonprotein calories. However, a minimum of 0.5 mg/kg/day is sufficient to prevent essential fatty acid deficiency.

Protein Requirements

The protein requirements for a mild to moderately stressed patient may be estimated at 1.5–2.0 g protein/kg based on ideal body weight. Although nonprotein calories may spare nitrogen in the nonstressed state, patients with cancer usually require an infusion of 0.2–0.3 g nitrogen/kg/day to maintain a positive nitrogen balance (174).

Fluid Requirements

Fluid requirements depend on baseline requirements, losses, and fluid deficits. Fluid status is dynamic and should be monitored on a constant basis by physical examination and accurate daily weights. The average fluid requirement varies from 1250 to 3000 ml/day, depending on body habitus. The average semistressed patient requires approximately 35 ml/kg/day. A wide array of fluid abnormalities can be seen in cancer patients due to the disease process and therapies such as surgery, radiation therapy, and chemotherapy.

Electrolytes

Electrolytes are included in all parenteral nutrition solutions. Electrolyte requirements for patients with cancer are essentially the same as for patients with nonmalignant forms of disease. The electrolyte composition of TPN will be dependent on the hormonal milieu, GI, and pulmonary losses, disease state, and renal and hepatic function (19). In addition, treatment modalities (i.e., amphotericin B administration) can alter electrolyte requirements. Daily serum electrolyte measurements are important to customize the patient's daily nutritional prescription. Limitations exist for calcium, phosphorus, and magnesium in parenteral nutritional solutions. Calcium and phosphorus can form a precipitate if they are not compounded properly or if excessive amounts are added to the solution (175). The pH, temperature, and type of amino acid solution will also affect the compatibility of calcium and phosphorus (176). Hypophosphatemia may result from hyperalimentation without adequate supplementation. A minimum of 20 meq of potassium phosphate per 1000 kcal will usually prevent hypophosphatemia (177).

ENTERAL FEEDINGS

If the GI tract is intact and functioning, liquid formula diets are preferred. Oral supplements provide an excellent source of calories and protein to bolster a modest oral intake or as an adjunct to hyperalimentation. Unfortunately, cancer patients often suffer from anorexia, nausea, oropharyngeal obstruction, or central nervous system pathology and cannot meet their caloric needs despite a functioning intestinal tract. These individuals can benefit from tube feeding. Small pliable nasogastric tubes are available and well tolerated by most patients. Delivery methods can be by either bolus feeding, gravity, or mechanical pump systems. In the critically ill patient, the literature supports the use of continuous rather than intermittent tube feeding. In this population, continuous tube feedings have been associated with positive nitrogen balance and weight gain as compared to intermittent tube feedings (178). Continuous tube feedings require less energy expenditure because of diet-induced thermogenesis and have been shown to be effective in the prevention of stress ulceration (179,180).

Although most patients' needs can be met with one or two enteral formulations, there are a myriad of diseasespecific products available. Slow rates should be initiated at 10–20 ml/hour and then increased 10 ml every 8–12 hours until full flow rates are obtained. There is usually no reason to dilute low-fat, well-tolerated formulas such as Peptamen, Vital, or Vivonex. The patient's head should be maintained at a 30° elevation with nasogastric and nasoduodenal feedings to avoid aspiration. For patients needing chronic enteral feedings, surgical or endoscopically placed gastrostomy or jejunostomy tubes may be beneficial.

Nutritional Adjuncts

Insulin has been investigated as an anabolic agent in the treatment of cancer cachexia because of the tumor-associated alterations in carbohydrate metabolism and insulin resistance demonstrated in cancer patients. Studies have shown that parenteral nutrition administered with insulin to cancer patients results in improved skeletal muscle protein synthesis and whole-body protein net balance compared with standard TPN (181). The use of insulin as an anabolic adjunct to TPN appears promising, but further trials examining clinical outcomes are needed.

Growth hormone has been shown to attenuate the loss of body protein when administered to patients without cancer (182). There has been little study of growth hormone as a nutritional adjunct in patients with cancer because of the fear of stimulating tumor growth. In animal studies and *in vivo* human tumor studies, no increase in tumor volume has been reported (183,184). Further studies will be needed to outline a potential role for growth hormone in the nutritional therapy of cancer patients.

Glutamine is a nonessential amino acid that has been noted to be depleted in patients with cancer. Standard TPN solutions do not contain glutamine because of instability issues. Addition of glutamine to TPN formulations has been shown to improve nitrogen balance and promote protein synthesis without stimulating tumor growth (185). Ziegler and colleagues in a double-blinded prospective trial found that patients receiving glutamine-enriched TPN had an improved nitrogen balance, fewer infections, and short-ened length of hospitalization compared with controls (186). Further clinical studies using glutamine are ongoing, as it may be potentially beneficial as an adjunct to conventional TPN in cancer patients.

Immunonutrition in Cancer Patients

Over the past several decades, our appreciation of the importance of feeding patients who are unable to take in calories adequate for metabolic requirements has increased extensively. Better techniques for providing nutrition intra-venously have improved the survival of patients with prolonged or permanent loss of GI tract function (187). Special enteral diets have been formulated to contain high amounts of arginine together with omega-3 fatty acids, nucleic acids, and sometimes glutamine (188). All these substances have been shown to enhance or preserve host immune responses and/or to reduce harmful and exaggerated inflammatory responses. This therapeutic approach has been termed immunonutrition (189).

Artificial nutrition support after major surgery should be considered an essential part of postoperative care. In particular, in patients undergoing pancreaticoduodenectomy or gastrectomy for cancer, early postoperative nutrition support is needed because, in these subjects, adequate post-operative oral intake is reached late, and preoperative protein-energy malnutrition is often present (190). Hochwald et al. reported in a randomized, prospective trial, that early postoperative enteral feeding led to a decrease in fat oxidation and protein catabolism. These findings were associated with hyperinsulinemia, which correlated with positive protein net balance. By significantly impacting on protein loss, early postoperative enteral nutrition may potentially contribute to a decrease in postoperative morbidity and mortality in upper GI cancer patients (191).

Since 1990, standard enteral and parenteral preparations have been modified by adding immunonutrients (192,193,194,195 and 196). This new category of dietary compounds has peculiar properties. Among the most interesting and carefully investigated immunonutrients are the following: (a) arginine, which improves macrophage tumor cytotoxic effects, bactericidal activity, and vasodilatation through production of nitric oxide; stimulates T-cell proliferation, natural killer cell cytotoxic effects, and generation of lymphokine-activated killer cells; and modulates nitrogen balance and protein synthesis (197,198); (b) omega-3 polysaturated fatty acids, derived from fish oil, which are potent anti-inflammatory agents through pathway of coagulation, and up-regulate the immune response; and (c) glutamine, which is known to facilitate the transport of nitrogen between organs, reduce the skeletal and intestinal protein waste during stress, enhance macrophage and neutrophil phagocytosis, and preserve the intestinal permeability by being the major fuel for different cell types (199,200). Glutamine administration helps minimize atrophy of intestinal mucosa associated with TPN, and intestinal mucosa damage due to chemotherapy and radiation therapy (201,202). Supplementation of the amino acid glutamine, by the enteral or parenteral route, as either the free or dipeptide form, appears safe and efficacious in patients undergoing BMT (203,204).

Prebiotic bacteria, such as *Lactobacillus plantarum,* seem not only to preserve key nutrients, such as omega-3 fatty acids, but also increase its content during storage conditions. *L. plantarum* competes with gram-negative potential pathogens for receptor sites at the mucosal cell surfaces, eliminates nitrate and produces nitric oxide; this may help recondition the GI mucosa. To produce a *L. plantarum*–containing formula, a treatment policy is regarded as an extension of the immunonutrition program, and is called *ecoimmunonutrition.* Patients with radiation therapy or cancer are candidates for ecoimmunonutrition (205).

The conception of immunonutrition has gained a great deal of clinical attention, and studies have been performed in an attempt to demonstrate clinical outcome benefits (189). In cancer patients undergoing elective surgery, Daly et al. reported, in two different studies, a significant reduction of postoperative infections in patients who were given immunonutrition early after surgery (206,207). A multi-center study from Germany showed a slight reduction in overall postoperative complication rate in the immunonutrition group (22% vs. 31% in the control group) (208).

When the authors grouped complications occurring before or after postoperative day 5, the immunonutrition group had significantly lower incidence of late postoperative complications, whereas no difference was found in the early postoperative complication rate. These results seem consistent with the hypothesis that some days of feeding are necessary to improve the host defense and subsequently to reduce infections (209).

A second study performed by Senkal et al. was more compelling (210). Patients were randomized to receive 5 days of preoperative and 5 days of postoperative immunoenhancing diet (IED) and standard-enhancing diet (SED). For the evaluable patients, there was a trend toward a significant reduction in overall combined infections and wound complications (IED = 13% vs. SED = 24%, p = .08) and significant reduction in late (>3 days) complications (IED = 9% vs. SED = 21%, p = .04). The number of early complications was low (210). Heslin et al., who studied 195 patients undergoing elective cancer surgery, did not find a significant difference in postoperative infectious and noninfectious complications by comparing groups treated with either an early postoperative immunoenhancing diet or simple crystalloid fluid replacement (211). However, in the immunonutrition group, the average postoperative energy intake was 60% of the nutritional goal and only 30% was given with the immunoenhancing diet.

Kemen et al. reported that postoperative immunonutrition improved immune response late after surgery, probably because the amount of immunonutrients given in the first days after operation was too small to stimulate a prompt burst of immune response and, consequently, to improve outcome (212). The early postoperative administration of enteral immunonutrition compared with a control enteral diet significantly reduced both severity of infections and postoperative stay, while the reduction of postoperative infection rate was not significant (190,213).

Braga and coworkers reported that the provision of immunoenhancing substrates before surgery appears to play a key role in reducing postoperative infections by a substantial activation of the immune response (209). Their data suggest that perioperative immunonutrition is efficacious regardless of the baseline nutritional status of the patients. In fact, preoperative administration of immunoenhancing diets reduced postoperative infections also in well-nourished patients in whom a severe postoperative impairment of the host defense mechanisms has been reported (214).

Galban et al. reported that immunoenhancing enteral diet reduced mortality rate and episodes of bacteremia in septic intensive care unit patients (215). In a prospective study by Fan et al., it was reported that perioperative nutrition support in the form of a solution enriched with branched-chain amino acids, dextrose, and medium-chain triglycerides was beneficial in reducing postoperative morbidity in patients undergoing major hepatectomy for hepatocellular carcinoma, especially when the liver was cirrhotic (216). Braga et al. reported that perioperative administration of immunonutrition ameliorated the host defense mechanisms and controlled the inflammatory response in patients with gastric cancer (217).

Another trial conducted by Snydermen et al. was more difficult to interpret because of poor study design and insufficient data in the manuscript. Patients scheduled for resection of head and neck cancers were randomized into four groups: (a) preoperative and postoperative IED, (b) postoperative IED, (c) preoperative and postoperative SED, and (d) postoperative SED. Thirteen patients were withdrawn from the study very early; of the remaining 129 (which are called the “intent to treat” group), 82 were randomized to the IED group, but only 47 to the SED group. Thirty-three of these patients failed to receive the correct formula. This left 85 patients who “actually fed” the correct therapy. In the “actual fed” group analysis, patients who received the IED had significantly fewer complications. This was also true for the “intent to treat” group analysis (218,219).

Meta-analysis provides the best estimate of overall treatment effect. In two published meta-analyses of immunonutrition, different investigators came up with different estimates of the overall effect on mortality. Heys and colleagues combined 11 randomized trials of immunonutrition in critically ill and surgical patients (220). Working with the data set that these investigators used, the effect on mortality was consistent with more harm than good, although the meta-analyses did not include several key papers published in non-English journals, published subsequent to 1998. Subsequent to this publication, Beale and colleagues aggregated the results of 12 randomized trials of immunonutrition in surgical and critically ill patients. Although there was some overlap between the two meta-analyses, the study by Beale et al. included recently published studies but was limited to studies of Impact (Novartis Nutrition Corp., Bern, Switzerland) and Immun-Aid (McGaw Inc., Irvine, CA) (221). Both meta-analyses concluded that use of IEDs had no significant effect on mortality rate (222). Moreover, Impact and Immun-Aid, the two enteral feeding preparations enriched with these “immunonutrients” that have been developed commercially for critically ill patients (Table 68-9), are slightly different in composition (221).

	Impact	Immun-Aid
Calories (kcal)	1000	1000
Protein (g)	56	37
Arginine (g)	12.5	14
Glutamine	—	9.0
Branched-chain amino acids (g)	—	20
Nudeic acids (g)	1.23	1.0
Fat (g)	27.8	22.0
Omega-3 polyunsaturated fatty acids (%)	10.5	4.5
Osmolality (mOsm/kg)	300	460
Vitamin C (mg)	67	60
Iron (mg)	12	9
Zinc (mg)	15	26
Selenium (μg)	46	100
Copper (mg)	1.7	2

Data from Beale RJ, Bryg DJ, Bihari DJ. Immunonutrition in the critically ill: a systemic review of clinical outcome. *Crit Care Med* 1999;27:2799–2805, with permission.

TABLE 68-9. COMPOSITION OF ENTERAL FEEDS IMPACT AND IMMUN-AID

It is unlikely that there are adverse effects of immunoenhancing nutrients given the modest amounts of the nutrients that are in the enteral formulas and the relatively short period (e.g., a period of weeks) patients are fed formulas with immunoenhancing nutrients. However, any nutrient that can alter immune function needs to be critically evaluated for potential adverse effects. Certain lines of breast cancer cells may also be stimulated to replicate when large doses of either L-arginine or L-glutamine are administered (223,224). It has been hypothesized that nitric oxide synthesized from L-arginine triggers vascular smooth muscle dilation and could potentially promote septic shock (225). A sheep model of sepsis has demonstrated administration of excessively high amounts (e.g., 200 mg/kg/h) of L-arginine parenterally has adverse outcome (226). However, this dose of arginine would be equivalent to over 300 g/day for a 70-kg man, which is not possible with the levels found in immunoenhancing formulas (227).

It is difficult to expect improvement in outcome with such a limited intake of immunonutrients. Better metabolic and clinical results were obtained with perioperative administration of immunonutrients (214). Immunoenhancing nutrients in the correct dose given early for 5 to 7 days appear to be safe and promote beneficial outcomes in select patient populations (227). In conclusion, specifically the perioperative administration of the supplemented diet improved the synthesis of constitutive visceral proteins and significantly reduced the rate of postoperative infections and the length of stay in patients undergoing surgery for cancer (214).

Home Parenteral and Enteral Nutrition

Oral or tube feedings in the home setting are both financially and physiologically preferred over parenteral nutrition. However, patients who cannot tolerate oral or tube feedings may benefit from home TPN. The technology and science of nutrition support has flourished in the last 20 years but not without a significant increase in costs. It has been estimated that nutrition support accounts for approximately 1% of all health care dollars (228,229). As expected, most of these dollars are spent on hospitalized patients, but approximately 20% are spent on patients living outside the hospital (228). Half of these patients are nursing home residents and half reside at home. Twenty percent of home patients receive parenteral nutrition support and 80% receive enteral nutrition support (228). The cost for enteral feeding is estimated at $15,000/year with home parenteral nutrition support being at least 10 times as costly (229).

Patients with a curable malignancy, who require aggressive primary treatment causing anorexia, nausea, and/or ileus, may benefit from home nutrition support. Other indications for home nutrition support are patients who are “cured” from their primary cancer but are left with bowel dysfunction from irradiation or resection.

A voluntary patient registry, the North American Home Parenteral and Enteral Patient Registry, was formed in 1984 to follow clinical outcomes of home patients receiving home parenteral or enteral nutrition. There are approximately 204 programs with more than 10,000 home nutrition patients registered. The Oley Foundation has published outcomes information on patients registered to date (230).

For the individual deemed a candidate for home nutrition support, techniques used at home and in the hospital are essentially similar. In the home setting, the patient and the patient's family may take responsibility for solutions administered (231). For parenteral nutrition, central catheter administration is the preferred route for hyperalimentation. This allows provision of adequate calories and protein without large fluid volumes. If possible, a Hickman catheter is preferred because it has two Dacron cuffs that help secure placement and reduce the risk of ascending bacterial infection. Strict sterile technique is essential to reduce the risk of catheter infection and sepsis. Even with precautionary measures, the incidence of catheter-related sepsis is 4.5–11.0% (232). In addition to the traditional subclavian or internal jugular central venous access, peripherally inserted central catheters (233,234) can be inserted into the basilic or cephalic vein in the antecubital fossa and threaded into the superior vena cava. Peripherally inserted central catheter lines are safe and reliable central venous access routes for patients receiving parenteral nutrition, long-term antibiotics, and chemotherapy without the complications of pneu-mothorax or hemopneumothorax. For all patients with intravenous lines, close follow-up with a nutrition support team is important to monitor fever, fluid status, and electrolyte abnormalities. To improve quality of life, patients can have enteral or parenteral feeding cycled at night to allow mobility during the day.

CONCLUSIONS

It is well known that patients with malignancy have a high incidence of malnutrition and cachexia resulting from decreased intake as well as metabolic alterations due to the influence of the tumor. The clinician must not only identify those patients at risk for malnutrition but must also identify those who will benefit from nutrition support.

Routine use of TPN in patients with cancer has not been substantiated in the literature (235). The clinician must carefully assess the severity of malnutrition, treatment options, and potential quality of life in the cancer patient before opting to use nutrition support as an adjunctive therapy. Decisions regarding methods and aggressiveness of the nutritional intervention should be based on these issues as well. The enteral route is always preferable to TPN in terms of physiological response, immune competence, quality of life, and cost (236).

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ISSUES IN NUTRITION AND HYDRATION

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Modern living conditions and advanced health care have changed the way people die. In the United States, 78% of people live past the age of 65, and 75% of the elderly will be challenged by incurable, progressive, or disabling illnesses during the last year of life (1). In many cases, difficulty with eating and drinking will occur during these processes, making decisions about whether to provide artificial nutrition and hydration (ANH) common events in most hospitals and long-term care facilities (2,3,4,5,6,7,8 and 9).

For many people, when dying appears inevitable, the quality of remaining life and the quality of dying become more important than duration of life. The palliative care and hospice care movements have been strongly motivated by the perception of unnecessary suffering at the end of life from futile medical interventions and neglect of patient's and family's wishes or goals surrounding dying. For the past three decades, the courts have upheld the right to refuse life-sustaining treatment, and all states have enacted one or more statutes creating advance directives or other mechanisms to uphold these rights (10,11 and 12). Likewise, an ethical consensus regarding these rights has been well established. However, issues regarding ANH at the end of life have been less thoroughly resolved.

The medical community has been reexamining its practice regarding ANH at the end of life. Although there are still controversies and debates, health care providers should be able to make appropriate recommendations regarding ANH and provide effective patient-centered care. This chapter will discuss the major issues surrounding ANH at the end of life: legal and ethical consensus and controversies, complexity of ANH issues in a diverse patient population, current practice in different clinical settings, observational studies of ANH in terminally ill patients, and the importance of respecting the values of patient and family. Suggestions to improve management of ANH issues in terminally ill patients will be focused on good communication under an integrated end-of-life palliative care plan.

LEGAL AND ETHICAL CONSENSUS AND CONTROVERSIES

Despite long-standing ethical consensus regarding the right to refuse medical treatments, a persistent debate has surrounded forgoing ANH at the end of life. Ethical consensus holds that ANH is a medical treatment that can be refused like any other treatment (13,14,15 and 16). Most professional organizations concur with this consensus (17,18,19,20 and 21), although an alternative position holds that ANH constitutes basic care that must be provided, and does not distinguish this medical treatment from the provision of food and water (22,23 and 24). Although this position may be based in religious or other moral beliefs, it could also be influenced by misunderstanding of the medical aspects of ANH; specifically, it may be driven by the mistaken perception that forgoing ANH leads to a painful death (25,26 and 27). Likewise, there may be a failure to recognize the potential medical complications and resulting discomfort from ANH as delineated elsewhere in this chapter. In parallel with an increasing dialog within the literature in the past decade, some commentators for the alternative position, which favors the use of ANH in almost all circumstances of inability to eat and drink, allow for decisions to forgo this treatment when the burdens outweigh the benefits (28,29).

In addition to the general ethical consensus, a legal consensus has emerged that ANH may be refused like any other treatment. A series of appellate court cases in the 1980s (30) culminated in the *Cruzan* decision in 1990, which was the first “right-to-die” case that reached the U.S. Supreme Court (31). In this case, the family of a Missouri woman in persistent vegetative state (PVS) asked that her enteral feeding tube be removed and she be allowed to die, a choice denied by the Missouri Supreme Court. The U.S. Supreme Court ruled that ANH constitutes medical treatment that can be refused like other treatments, but held that the states can develop their own standards of decision making for the incompetent. In the case of Nancy Cruzan, lower courts had applied a strict evidentiary standard for. refusal of life-sustaining treatments and ruled that there was not “clear and convincing evidence” of the patient's wishes regarding withdrawal of her treatment, and the U.S. Supreme Court upheld Missouri's application of that standard. Since *Cruzan*, many states have developed additional methods of decision making for the incompetent, including laws with surrogate, decision-making provisions, which establish a hierarchy of decision makers who decide for incapacitated patients who lack advance directives (11). Although the “clear and convincing standard” was not applied specifically to ANH in the Supreme Court decision, many state statutes maintain separate and higher legal standards for ANH as compared with other life-sustaining treatments, or contain separate provisions regarding ANH that can be confusing or misleading (32). To date, there is no evidence that state-by-state variations in the use of tube feeding in patients who lack capacity correlate with specific legal standards (33). However, the persistence of separate standards raises concerns as to their constitutionality and could lead to misunderstanding on the part of patients and surrogates, as well as fear on the part of physicians that recommending the withdrawal or withholding of ANH might lead to legal repercussions.

It is noteworthy that none of the appellate tube-feeding cases involved people with cancer (30). Most involved people with PVS, perhaps reflecting the long duration of tube feeding in the persons whose cases were decided (average 3.5 years). In the experience of one patient advocacy organization, most disputes over tube feeding involve elderly patients with dementia (30). In that group of patients, disputes about life-sustaining treatments in patients with other serious illnesses, such as cancer and organ failure, generally involved life-sustaining treatments other than, or in addition to, ANH, even if ANH was currently being provided. Legal theory regarding ANH or tube feeding is generally based on a very specific type of patient—that is, one with a fixed or slowly progressive neurological deficit. This probably reflects the lower use of tube feeding (2) and shorter presumed prognosis or actual survival of patients with advanced cancer, and perhaps a greater acceptance by the health care team and family that death is inevitable in advanced cancer. It may also reflect a higher proportion of cancer patients who have decisional capacity and can be involved in the decision, and who would face fewer legal obstacles in the forgoing of ANH. In the patient with advanced dementia or PVS, medical and prognostic issues may lead to a perception that withholding or withdrawing ANH amounts to “killing the patient,” who might otherwise live for a prolonged period. In the case of the patient with advanced dementia, however, increasing evidence suggests that average life span is approximately 6 months (34,35,36 and 37) and ANH does not appear to affect the overall prognosis (34). It is likewise probable that ANH would not affect the overall prognosis in a patient with advanced cancer.

COMPLEXITY OF ARTIFICIAL NUTRITION AND HYDRATION ISSUES IN A HETEROGENEOUS PATIENT POPULATION

People die from different diseases, in different settings, with different levels of readiness, and different perceptions regarding good quality of dying, with different goals and wishes regarding their dying, and with different patterns, or “trajectories.” Confusion and controversy in the care of these patients, specifically with regard to ANH, can easily arise when patients are classified with a general term, such as “terminally ill” or “end of life,” without reference to a more specific stage, situation, or individual perception of quality of death.

Three Trajectories of Terminal Diseases

Most Americans will die from disabling, progressive, or chronic disease. Lynn has characterized three trajectories that patients generally follow before death (38). The first trajectory applies to the patient with “terminal cancer,” who usually can perform activities of daily living and preserve their decision-making capacity until quite late. Most of the studies examining the impact of dehydration and the role of artificial hydration in patients with terminal illness have been conducted in this group of patients (6,39,40,41,42 and 43). The second trajectory represents those dying mainly of chronic organ system failure such as heart, lung, renal, or liver disease. Such patients are usually very sick for months or years with recurrent exacerbations. The timing of death usually remains unpredictable until very late in the disease. Persons with

progressive disability, such as strokes, dementia, or general frailty accompanying very old age, follow the third trajectory; many of them are incompetent months or years before death. Most of the studies around tube feeding have been conducted in this group (25,34,44,45 and 46). The situation that the patient, family, and physician confront when they have to make decisions regarding artificial support of nutrition and hydration at the “end of life” can be quite different among these three groups of patients.

Defining Terminal Illness and the Dying Stage

The natural history of the common symptoms and signs present in terminally ill patients is not well characterized, and adequate staging systems are lacking (47,48). The concepts of “terminal illness” and “end of life” are vague, and there is no unanimity about their definition. Within the law, “terminal” may be defined loosely as death “imminent” or expected to occur in a “relatively short time,” or in a time-limited fashion (typically, 6–12 months) (49,50 and 51). In addition, “terminal illness” has been defined with respect to administration of life-sustaining treatments—for example, a condition that would result in death within 6 months *even with* administration of life-sustaining treatment (52), or one that would result in death within a relatively short time *without* the administration of life-sustaining treatment (53). Some of these definitions might be especially problematic when questions of ANH arise. For example, one could argue that ANH would postpone death beyond a specific time limit in certain circumstances, such as a severe neurological impairment, or that the person could not be considered “terminally ill” if this treatment were provided. Given the higher standards that often exist in the law regarding ANH, as noted earlier (see the section Legal and Ethical Consensus and Controversies), gaps exist between the body of law, on the one hand, and the diverse clinical scenarios that actually occur.

Prognostic uncertainties seen in patients with chronic organ system failure (the second trajectory) and patients with progressive disability (the third trajectory) have been recognized as the major barrier to enrolling these patients in hospice programs in a timely fashion (54,55), and could influence physician recommendations about lifesustaining treatments, especially ANH. Studies seeking to define or stage terminal illness have mostly used patients with cancer (the first trajectory). Vigano et al. conducted a systematic literature review on prognostic factors for survival in cancer patients considered to be terminal and found no standard criteria in the literature to define this phase (48). A predicted survival of 3–6 months is often the time when treatment goals change from curative to palliative (48,56,57), although the phase may actually last 12 months or so in some patients. However, physicians have a tendency to overestimate the final 3–6 months of survival (58,59,60,61 and 62). The uncertainty in estimating survival contributes to the difficulty in decision-making regarding ANH at the end of life. It also limits the rigor of studies on ANH, as patients are not uniform in terms of representing similar and specific (inception) points during the course of their disease.

Where the Patient Dies

In general, the majority of Americans die in a hospital (63,64,65 and 66). In 1994, 62% of all deaths in the United States occurred in hospitals, 16% in nursing homes, and 17% at home (66). Only 10% of dying patients were in hospice care (66), but in 1999, this rose to approximately 29% (67). Marked variations in the care of dying patients exist across geographical regions, depending very much on the local availability of hospital beds and the capacity of community heath care provider to meet the dying patient's needs (63). The majority of Canadians also die in hospitals (68). The setting can indirectly affect decisions about ANH because of the perceived lower urgency and importance of ANH compared to other treatments, the readiness of patient and family to accept the inevitability of death, and experience of the staff in handling these issues (4,5,64,69).

Attitudes, Values, and Culture of Patients, Families, and Health Care Providers

Attitudes about appropriateness of use or nonuse of ANH at the end of life are diverse, varying among patients, surrogate decision makers, and health care providers, and may be related to an individual's definition of quality of life, the individual's values and perceptions, and the ethnic or cultural background of dying patients and their families (57,70,71,72,73,74,75,76,77,78 and 79).

The cultural, religious, or ethnic background can influence the attitude of both patients and health professionals. For example, elderly Catholic patients at a Veteran's hospital appeared less willing to undergo tube feeding than other Christian patients in response to a hypothetical end-of-life scenario (74). Many studies have shown that black patients are more likely than white patients to desire life-sustaining intervention, including tube feeding (75,76,79,80,81 and 82). In a related study, black physicians were less likely than white physicians to consider tube feeding as “heroic” and more likely to request aggressive treatments, including artificial feeding for themselves if they were in PVS (78). In a survey of elderly Chinese attending a day care center in Singapore who were asked about life support measures at the end of life, 55.8% said they would want nasogastric feeding and 65.1% would want intravenous (i.v.) hydration (77). In an international study, none of the nurses in North America interviewed would “force-feed” a hypothetical elderly patient with incurable, advanced cancer who refused to eat, whereas all the Chinese nurses interviewed would feed such a patient (83).

Provision of accurate and thorough information can influence patients' attitudes and decisions. A recent study among a small group of family caregivers of patients in a palliative care program revealed diverse attitudes about hydration in terminal care (70). Without receiving information specific to hydration, some felt that hydration might enhance comfort in terminal dehydration, some thought that it might be a burdensome and useless procedure, and some were not able to identify advantages or disadvantages. One central factor was the individual's perception of benefits or burdens of artificial hydration for the dying. Other factors, such as their beliefs about life prolongation and the patient's previously stated preference, also influenced their attitudes. Nevertheless, most family caregivers thought that they would like to know from the physician the options, as well as the advantages and disadvantages of hydration, in the situation. Others would not be concerned with this information and would expect the medical professionals to make the decision (70). A 1994 survey of terminal care preferences in 108 gynecological cancer patients found 63% would consider continuing ANH in end-stage disease (71). Interestingly, 47% of those with active disease, compared with 28% of those with inactive disease, thought that they would withhold or withdraw ANH if this issue were to arise. However, in these hypothetical situations, it is not possible to know what the patient would want if death were a closer reality, if the scenario given were more specific, or if the physician's opinion about ANH at the end of life were given. In fact, a patient's attitude may sometimes be influenced by the information from the doctor. For example, in a recent survey of 379 randomly selected, decisionally capable residents from 49 nursing homes, 33% stated they would prefer tube feedings if no longer able to eat because of permanent brain damage; but 25% of the latter changed their preference on learning that physical restraints are sometimes applied during the tube feeding process (79). The impact on patient decision making of information about a treatment's potential burdens or lack of survival value has been demonstrated in other situations, such as do-not-resuscitate decisions (84). Thus, fundamental “attitudes” and “values” of patients and surrogates cannot be ascertained unless accurate information is provided.

CURRENT USE OF ARTIFICIAL NUTRITION AND HYDRATION IN PATIENTS WITH TERMINAL ILLNESS

Artificial Hydration in Acute Hospitals

Depending on the type of facility where the patient dies, the practice of ANH among patients in their last few weeks or days of life can be quite different. The emergence of palliative care has increased the awareness among physicians in the acute setting to identify those who are dying and to switch the treatment goal to comfort care as soon as possible (7). However, most patients dying in the hospital continue to receive i.v. fluids (4,5,68,72).

Alpert et al. reviewed 7400 inpatient records between 1987 and 1989 in a Boston teaching hospital and identified 181 patients with coma and a small chance of recovery, dementia with coexisting terminal illness, or PVS (72). Of these patients, 70% continued to receive artificial hydration. A multiinstitutional study of 229 patients dying from 1989 to 1992 in four Minnesota hospitals showed that 53% were given i.v. fluid at the end of life (5). These proportions do not include 16% who had i.v. fluid withheld (5). A Canadian study found that continuous i.v. fluid was used in 90%, 63%, and 28% of the patients dying from 1992 to 1993 in a large acute hospital, two small acute hospitals, and one continuing care facility, respectively (68).

Terminally ill patients admitted to a hospital usually have acute and potentially reversible illness, and these conditions may be aggressively treated until very late in the course of the underlying illness. A chart review of 200 consecutive adult deaths in a New York City teaching hospital found that physicians identified 72% of patients as dying during the hospitalization (7), but they were identified as dying an average of 8.7 (median, 4.5) days from admission and 9.6 (median, 3.5) days before death. Only 64% of those identified as dying had a comfort care plan, and this was put in place an average of 15 days after admission despite a 17-day overall mean length of stay. Very often, when the patient is identified as dying in an acute hospital, invasive, life-sustaining treatments, including ANH, may already be in place. In such a situation, the major decisions by physicians and families, not surprisingly, focus on cardiopulmonary resuscitation, ventilator, pressor use, pain control, transfusions, and dialysis, rather than ANH (4,72). In fact, withholding resuscitation is generally the first step in decisions to limit treatment, whereas i.v. fluids and tube feeding are forgone relatively rarely or late in acute hospital practice (4,72,85,86).

Artificial Hydration in the Palliative Care Setting

Most patients enrolled in palliative or hospice care have advanced cancer (87). For these patients, the overall goal of comfort care has already been established and decisions about cardiopulmonary resuscitation, ventilator, and dialysis usually have been settled. If such patients do not die quickly from superimposed acute illness, such as hemorrhage, infection, or a cardiovascular event, they may progressively reduce oral intake because of growing weakness, anorexia, multiple comorbidities, delirium, or disease progression, and will soon die regardless of whether parenteral fluid is given. Palliative care professionals with extensive clinical experience in end-of-life care generally believe that the symptoms of terminal dehydration per se are mild, can be managed by simple mouth care, and that artificial hydration is

usually unnecessary for symptom control in dying patients (88,89). This approach is supported by some empirical observational studies (39,40 and 41). However, others in palliative medicine maintain that dehydration may sometimes have undesirable consequences, such as confusion or potentiation of opioid toxicity, and they routinely use subcutaneous hydration or rectal hydration when dying patients are not able to take in the minimal daily requirement (90,91 and 92). These types of artificial hydration are different from traditional, continuous, larger-volume i.v. infusion that has been criticized by many authors in the past, and observational studies showed that patients tolerated the nontraditional approaches well (90,91 and 92). But there are no controlled studies that have evaluated the advantage of using any form of artificial hydration for patients dying of cancer or other illness (see below).

Enteral Tube Feeding in Elderly Patients with Advanced Disease

In the United States, the number of elderly receiving percutaneous endoscopic gastrostomy (PEG) increased from 15,000 to 123,000 between 1989 and 1995 (45). In nursing homes, 7–40% of residents with severe dementia have feeding tubes (33,93,94). Tube-fed elderly are mostly patients with advanced diseases associated with dysphagia, anorexia, aspiration pneumonia, or malnutrition (80,95). Many of these elderly patients died soon after feeding tubes were placed (45,80,95,96).

A large proportion of patients who die in hospitals have a feeding tube in place. In the Boston study previously cited (see the section Artificial Hydration in Acute Hospitals), 27% of the 181 patients in the terminal phase of life received artificial nutrition (72), and the above-cited Canadian study (68) (see the section Artificial Hydration in Acute Hospitals) found that tube feeding was used in 85%, 58%, and 40% of patients dying in a large acute hospital, two small acute hospitals, and one continuing care facility, respectively. A recent study in a New York City teaching hospital found 51% of dementia patients and 11% of cancer patients had a feeding tube in place at death (2).

There are geographical and international variations in the use of tube feeding. A recent nine-state survey of elderly who had very severe cognitive impairment and resided in nursing homes during 1994 found significant interstate differences in the prevalence of tube feeding, ranging from 7.5% in Maine to 40.1% in Mississippi (33). Among severely demented patients in Kansas, those in urban nursing homes were almost three times as likely to have a feeding tube than those in rural ones (46). An international study (97) found that tube-fed patients were more likely to have a diagnosis of dementia (60.4% versus 10.9%, p <.001) and less likely to have had a stroke (35.4% versus 71.7%, p <.001) in Boston than in Ottawa. Also, decisions to insert feeding tubes in nursing home patients were significantly more like to be made in Boston than in Ottawa (68.7% versus 6.5%, p <.001).

OUTCOME STUDIES OF ARTIFICIAL NUTRITION AND HYDRATION IN TERMINALLY ILL PATIENTS

Over the last two decades, controversies have continued over whether artificial hydration is necessary to enhance comfort in dying patients. Most of our knowledge in this regard has been derived from studies on terminally ill patients with advanced cancer in palliative care settings. In contrast, controversies regarding enteral feeding tubes have been mostly focused around patients with advanced neurological diseases, such as severe dementia, and have addressed the question of whether tube feeding would reduce the incidence of aspiration pneumonia or prolong life. However, with regard to all of these questions, prospective, randomized, controlled trials are lacking and would be extremely difficult to perform in terminally ill patients. All existing data to date come from retrospective or observational studies. In the absence of rigorous controlled studies, however, descriptive observational studies remain valuable and have revealed some useful information.

Do Symptoms Such As Thirst and Dry Mouth Correlate with Fluid Status or Fluid Therapy in Dying Patients?

Healthy subjects, especially the non-elderly, generally develop troublesome symptoms with dehydration. Symptoms vary from thirst, dry mouth, muscular fatigue, nausea, abdominal pain, loss of appetite, headache, irritability or drowsiness during mild dehydration (1–5% body water loss), to trembling, trouble sleeping, progressive obtundation or delirium with more severe dehydration (6% or more body water loss) (98).

Patients with terminal illness suffer many physical and psychological symptoms from various conditions, even without dehydration. Symptoms seen in dehydrated healthy persons, such as dry mouth/thirst, anorexia, vomiting, drowsiness, and confusion, each occur in one-third or more of terminally ill patients (98). In some studies, thirst or dry mouth occurred in 66–95% of dying patients who could respond to questions (40,63,99). However, these symptoms are very nonspecific, and in dying patients, it is difficult, if not impossible, to distinguish them from symptoms that may be due to their underlying disorders, medication, the oral condition, or unknown mechanisms of the dying process. Indeed, in terminally ill patients, a cause-effect relationship between dehydration and these symptoms has not been established.

There is no consistent relationship between thirst/dry mouth and fluid status or fluid therapy (40,51,99). In a carefully designed study of symptoms associated with dehydration in 52 terminal cancer patients in an inpatient palliative care setting, Burge found a high incidence of thirst, dry mouth, bad taste in the mouth, and fatigue (100). However, there was no correlation between these symptoms and quantified fluid intake, metabolic abnormalities, or use of drying medications. Mean and median serum sodium, osmolality, and urea were within normal limits. Half of the patients were excluded from the study because of drowsiness, confusion, or weakness. Ellershaw et al. observed 82 dying cancer patients in a hospice setting with median time of 2 days from entry into the study until death (range, 1–5 days) and showed no significant relationship between respiratory tract secretions and the level of hydration based on laboratory data (40). For those who were able to respond to questions (28%), no correlation between level of hydration and thirst/dry mouth was demonstrated. All subjects died without artificial hydration. Serum samples obtained at the entry point had a mean osmolality of 289 mOsm/kg, with more than 50% being less than 295 mOsm/kg. Musgrave et al. followed 30 patients in the last 24 hours of life in a hospital oncology unit who died while receiving i.v. fluids to assess the effects of these fluids on their level of thirst (99). Of the 19 patients who were able to verbally respond to questions, 18 had various degrees of thirst in spite of i.v. hydration, and 70% had clinical signs of fluid retention. No relationship was found between the degree of thirst and the amount of i.v. fluids received, serum sodium, or blood urea nitrogen.

Can patients with terminal cancer die comfortably without ANH? Experienced hospice physicians have long believed that dying patients do not require ANH for comfort (88,89). Lately, some empirical studies have reported the same conclusion, showing that thirst and dry mouth can be relieved by careful mouth care, sips of water or ice, and voluntary oral intake if the patient desires (39,41,42).

McCann and his colleagues followed 32 terminally ill patients in a comfort care unit in a long-term care facility (39). Most of the patients had cancer, and all were initially able to report symptoms. The goal of the study was to determine whether hunger, thirst, and dry mouth in terminally ill patients could be palliated without ANH. Comfort measures included offering oral nutrition and liquids at the patient's request, careful mouth care, and standard treatments for other symptoms (e.g., opioids for pain and dyspnea). Many of these patients were able to consume fluids or food initially. Twenty patients (63%) never experienced any hunger, while 11 patients (34%) had hunger only initially. Thirst or dry mouth was present in about one-third only initially and in another one-third until death. In all patients, symptoms of hunger, thirst, and dry mouth could be alleviated, usually with small amounts of food and fluid by mouth, or by the use of ice chips and lubrication to the lips. Twenty-seven (84%) of the patients were judged to be comfortable with regard to hunger, thirst, or dry mouth during the stay. The average length of stay until death was 40 days (range, 4–199 days). Thus, this observational study provided direct evidence that it may not be necessary to provide ANH for those terminally ill patients who gradually lose desire or capacity to eat or drink in order to assure their comfort.

Vullo-Navich et al. recently published a prospective study at an inpatient hospice unit of a Veteran's Hospital (41), observing the spontaneous, oral fluid–intake pattern of dying cancer patients who did not receive parenteral fluid. Only 31 (26%) of 116 patients admitted to the unit were studied, usually because the patient died before consent could be discussed. The length of stay from entry point to death ranged from 2 to 35 days with an average of 15 days (median of 13 days). Among the 31 cases, 19 (61%) met the clinical criteria of dehydration (drinking less than 500 ml of fluid per day for 2 consecutive days) before death. The most common symptom was dry mouth, which was easily relieved with local measures, similar to previous studies (39,42,89). The level of comfort was scored from 1 (uncomfortable) to 4 (comfortable). Scores from three nursing shifts were summed to create daily comfort scores ranging from 3 to 12. A perfect comfort score was realized in 85% of the 678 patient days and there was no significant difference between mean comfort scores for the period before and after the appearance of dehydration. This observation reinforces the belief that fluid depletion in dying cancer patients does not produce adverse symptoms, and that comfort can be maintained without artificial hydration in the last few days of life. This is important information to share with the patient and the family.

Does Artificial Hydration Improve Delirium in Dying Patients?

Terminal confusion or delirium is very common. According to prospective data on patients with advanced cancer, the occurrence rate of delirium ranges from 28% to 42% among patients newly admitted to a palliative care unit and is as high as 88% before death (101,102). Delirium in terminally ill patients may generate extreme distress for some patients, as well as their families and caregivers (102,103 and 104), and it is usually treated by increasing the dose of sedation (105,106,107 and 108). Although natural or sedation-induced coma in terminally dehydrated patients is believed to promote a “peaceful death” (109,110 and 111), some commentators have raised the concern that patients and families might wish to avoid deterioration in cognition if this would prevent meaningful interaction with family and friends (102,103,112,113). A national survey showed that being mentally aware at the end of life was rated as important by 92% of randomly selected veterans with advanced chronic illnesses who had been hospitalized for these diagnoses within the prior year, but was so rated by only 65% of the physicians in the survey (114).

The causes of “terminal confusion” or “terminal delirium” are multiple (102). There may be differences between typically described delirium—a transient and potentially reversible condition—and “terminal delirium” that is often seen in the last few days or hours of life (102). Some hospice specialists have questioned whether we fail to identify some cases of reversible delirium because we assume that death is imminent (102). Some have advocated vigorous screening for mental status changes and evaluation for possible reversible and treatable causes (91,103,115). Lawlor et al. recommended recently that when the care goals of dying patients include preference

to treat delirium by attempting to reverse it, the standard approach should involve searching for reversible causes and providing specific symptomatic treatment for delirium to avoid premature initiation of deeper sedation (102).

Dehydration can be one of the potentially reversible causes of delirium in some dying patients. However, whether hydration can improve mental status of a dehydrated cancer patient who is dying from the underlying disease is not clear. Waller et al. assessed 68 hospice patients during the last 48 hours of life to correlate various measures of hydration with their level of consciousness (42). Nearly all of the patients had dehydration based on laboratory data, and the level of consciousness correlated inversely with serum sodium and urine osmolality. However, those who were treated with i.v. fluids (13 cases) did not have improvement in their level of consciousness. It is possible that underlying conditions and not dehydration alone are largely responsible for the reduced mental status of these patients.

Pereira and colleagues (115) evaluated data on 321 patients with advanced cancer and severe symptoms who were admitted to a hospital palliative care unit where Mini Mental State Examination (MMSE) was routinely conducted in all the patients on admission and once or twice weekly thereafter. Because of visual or motor deficits preventing some patients from performing the entire MMSE, the results are expressed as percentage of 1. Scores of less than 0.8 were considered consistent with cognitive impairment and patients underwent further assessments, including delirium evaluation. When delirium was diagnosed, a standard protocol was followed to assess possible dehydration, opioid toxicity, infection, brain metastases, uremia, hypercalcemia, and hypoxia. Efforts were made to correct these underlying causes when possible and appropriate. The mean length of stay was 27 ± 22 days with a median of 20.5 days. Of 87 patients, 25 (29%) with abnormal MMSE on admission improved to a normal score on final testing before death (N = 13) or discharge (N = 12). Time between admission and the first normal MMSE score averaged 10.3 ± 9.4 days (range, 1–36 days; median, 7 days). However, there are no details about the causes of the delirium, and the contribution of hydration to the improvement of these patients' mental status is not clear from the study.

Some palliative care clinicians and researchers have argued that neurological symptoms in dehydrated terminally ill patients who receive high doses of opioids might be prevented by appropriate hydration and opioid rotation (6,91). The rationale behind this is that dehydration reduces intravascular volume and glomerular filtration and thus may slow renal elimination of active opioid metabolites (116,117 and 118), the accumulation of which can cause agitated delirium and myoclonus (116,117 and 118). Fainsinger and Bruera suggested gentle hydration by using subcutaneous hydration (hypodermoclysis) or rectal hydration (proctoclysis), in addition to opioid rotation, in terminally ill patients who are not able to take adequate fluid orally (6), noting that agitated delirium in their palliative care unit reduced from 26% to 10% after they changed the practice to more frequent use of hypodermoclysis (91). Other changes in their practice, however, such as switching opioids earlier if toxicity developed and the use of less toxic antipsychotic agents, may also have contributed to the reduction of agitated delirium. Randomized, controlled studies are needed to confirm whether clysis or other forms of artificial hydration would reduce agitated delirium and reduce the need for heavy sedation.

Does Enteral Tube Feeding Reduce the Risk of Aspiration Pneumonia or Prolong Life in Elderly Patients with Advanced Disease?

Like research on artificial hydration in terminally ill patients, there have been no randomized controlled studies examining the outcome of feeding tube placement. Studies in this regard are usually conducted in elderly patients who received gastrostomy tube placement, but not in those specifically defined as being terminally ill. Retrospective reviews or prospective observations, so far, have failed to demonstrate that tube feeding can reduce the risk of aspiration pneumonia (25,44,119,120,121,122 and 123), and jejunostomy does not do better than gastrostomy in this regard (124,125). Studies on the outcome of those receiving feeding tubes have consistently shown a high short-term mortality rate. A national study of 7369 veterans who received a PEG tube from 1990 through 1992 reported a mortality rate of 23.5% during the hospitalization in which the PEG tube was placed. The median survival of the whole cohort was 7.5 months (95). Another study of 81,105 older Medicare beneficiaries who received gastrostomy insertion following hospital discharge in 1991 revealed an overall mortality rate of 23.9% at 30 days, and 63.0% at 1 year (80). A prospective cohort study in an Indiana community of approximately 60,000 residents identified 150 patients age 60 and older receiving PEG from November 1997 to January 1999, and found a 30-day mortality of 22%, and a 1-year mortality of 50% (45).

More recently, commentators have questioned the benefit of tube feeding in older patients with severe dementia. In a recent study of acutely hospitalized patients with advanced dementia in a New York City teaching hospital, 50% received a new feeding tube during the index hospitalization (34). With or without a feeding tube, these patients had a 50% six-month median mortality (34). As noted above (see the section Enteral Tube Feeding in Elderly Patients with Advanced Disease), the prevalence of feeding tubes in nursing home patients with severe dementia is very high. In one study, the 1-year mortality rate for older nursing home residents who received PEG tubes was about 50% (96). Retrospective and observational studies in severely demented patients with chewing and swallowing problems also failed to show the benefit of survival in those receiving tube feeding (93,94).

The high mortality rate after gastrostomy tube placement shows that many of these patients were actually near death when feeding tubes were placed and suggests that the indications for its use should be reexamined (126,127). Since survival varies greatly among patients who receive feeding tubes, it would be inappropriate to apply population data to individual patients. The impact of baseline diseases and functional status on the prognosis of an individual patient, and the potential burdens and complications of tube feeding, should be strongly considered in the decision process (126,127).

Biomedical Approach Is Not Enough

Biomedical studies, such as those discussed above, are very important because they can help to provide information about pathophysiological changes in dying patients and their physical responses to our interventions, which is information we need to share with patients and families in end-of-life care planning. However, the suffering of dying patients and their loved ones is far more than physical (114,128,129). Unfortunately, physicians may tend to judge the outcome by biomedical parameters and pay less attention to the perspective of patient and family (114,128,129 and 130).

It has become more clear that the clinical usefulness of medical interventions cannot be justified fairly without consideration of the emotional and psychosocial concerns of patients and their families (47,65,131,132). For example, observational studies have reported that comfort could be achieved in dehydrated, terminal-cancer patients treated in facilities with policies of generally avoiding artificial hydration (39,40) or providing carefully monitored hypodermoclysis or proctoclysis to almost all dying patients (6,90,91). The patients and their families in these studies seemed to accept either approach quite well. This suggests that it may not be the avoidance or provision of artificial hydration that makes the patient and family comfortable and satisfied. The atmosphere of the care setting, the attitude of the staff, the quality of the interpersonal relationship and communication between staff and patient and family, and the overall care plan may all contribute to the success of these approaches.

IMPROVING COMMUNICATION AND MANAGING ARTIFICIAL NUTRITION AND HYDRATION-RELATED ISSUES UNDER A COMPREHENSIVE END-OF-LIFE CARE PLAN

Promotion of quality of life and quality of death as defined by the patient and family are finding their way into all aspects of health care, especially at the end of life (1,47,65,114,128,131,133). Even for a non-dying patient, a good technical or biomedical outcome doesn't always guarantee acceptable quality of life and patient satisfaction (134). Whether to use ANH in the terminally ill is neither strictly an ethical nor strictly a biomedical issue. For a specific patient, the issue should be managed as part of a good, comprehensive, patient-centered, and family-sensitive care plan, and, as with any end-of-life treatment, communication is critical in care planning. However, open doctor-patient communication about end-of-life treatment may be rare or late (135,136,137 and 138). Discussion about ANH in terminally ill patients may be even less common, or in haste and late in the course (9,70). The disparity of views in quality of death between physicians and patient or family (114,128,139,140), the various attitudes of patients (57,70,71 and 72,136) and physicians (6,141) about ANH, and lack of understanding on the part of patients regarding their options in end-of-life care (142) all highlight the need to improve communication about this particular treatment.

Physicians should initiate end-of-life discussions early and incorporate ANH issues into the discussion. Even patients who express their wishes and values very clearly still may need the physician to initiate the discussion (138,143). Listening and knowing the patient's and family's values, concerns, and level of understanding are critical (138). It is also important to make sure patient and family understand their legal rights and the ethical consensus surrounding the use or nonuse of ANH to ensure that their own values and preferences will be respected, and that efforts will be made to relieve suffering. However, the upholding of the patient's right to choose from among care options is insufficient if the patient or surrogate does not fully understand the benefits and risks of these options (1,138). In the experience of the authors, patients and loved ones may fail to ask whether ANH must be given and are often unaware that it can be avoided, or discontinued, and what the consequences are. Therefore, health care professionals should be mindful of this “unasked question” and should provide accurate information regarding what is known about the benefits and burdens of ANH and the likelihood that a particular patient can be kept comfortable without it. It is also important to enumerate the potential alternatives to ANH in the patient in question (10). For example, small amounts of desired food and fluids can be given at the patient's request. This is a potentially comforting alternative to ANH, and family and friends can take an active role, which may be comforting for loved ones as well. Dietary restrictions (such as salt avoidance for fluid retention, or sugar restriction for diabetes) should be avoided, if at all possible, and personal and ethnic food preferences should be addressed. If a decision is made to start artificial hydration or to institute tube feeding in a terminally ill patient, there should be a specific goal in mind, and the physician and patient or surrogate should be prepared to reevaluate periodically the appropriateness of continuing it.

Appropriate and timely discussion of ANH issues in the planning of end-of-life care may avert a stressful, decisionmaking dilemma when the patient reaches the final stage of dying. Early discussion and planning for care options may also leave more time and may enhance the ability of the patient and family to work on more important issues of life closure (137,138). Good communication, which can itself be emotionally and spiritually healing (138), along with a good patient-centered and

family-sensitive end-of-life care plan (65), will maximize the likelihood of achieving the patient's goals.

SUMMARY

Increasing longevity has been accompanied by a risk of dying from incurable, progressive, and disabling chronic diseases such as cancer or dementia. Decisions around use or nonuse of ANH at the end of life have become common events in medical practice. A broad, legal, and ethical consensus supports a patient's right to decide whether to accept or refuse ANH as part of his or her end-of-life care. Meanwhile, arguments around the palliative effect of ANH in terminal illness continue. The issues are complicated by the broad spectrum of terminal illness (“trajectories of dying”), the various settings in which dying occurs, and persisting statutory provisions regarding ANH that may create confusion among providers and patients. Issues are further confounded by individual attitudes, values, and cultural backgrounds. Attitudes can be dependent on the provision of accurate information about the benefits and burdens of this treatment. Despite the lack of randomized, controlled studies, findings in retrospective and observational studies still provide some useful information. Physicians should not shy away from sharing the information and making recommendations, while at the same time paying attention to the values of the patient and family. ANH discussions should be incorporated early in end-of-life care planning. Good communication and a patientcentered and family-sensitive end-of-life care plan is the key for successful management of the complex issues surrounding this treatment.

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70

REHABILITATIVE MEDICINE

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Patients with progressive medical diseases often benefit from physical rehabilitation. Referring to the cancer population, Dietz described four levels of rehabilitation: palliative, supportive, restorative, and preventive (1). In palliative rehabilitation, efforts are made to decrease dependence on others in activities of daily living (ADLs) and to provide comfort and emotional support. This approach is most appropriate for patients with advanced disease and short life expectancies.Supportive rehabilitation is focused on long-term impairments. Efforts are directed at maximizing function at any given level of disability. When impairment is expected to be short-lived, restorative rehabilitation is appropriate. These techniques, which are intended to return the patient to a previous level of function, may be very useful when function is impaired because of a side effect of cancer treatment (e.g., myopathy caused by corticosteroids). Preventive rehabilitation may be valuable when impairments are anticipated and interventions may be able to prevent them. For example, a simple exercise program for the patient fatigued by radiation therapy may prevent deconditioning.

Three terms are commonly used to describe physical, functional, or psychological deficits: impairment, disability, and handicap. *Impairment* is defined as “any loss or abnormality of psychological, physiological or anatomical structure or function” (2). *Disability* is “any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being” (2). *Handicap* is “a disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfillment of a role that is normal (depending on age, sex, and social and cultural factors) for that individual” (2). Thus, an impairment may result in a disability, which in turn may give rise to a handicap.

SPECTRUM OF FUNCTIONAL IMPAIRMENTS

Functional impairment in the patient with cancer may arise from many causes (Table 70-1). Cancer may directly produce physical impairments that require rehabilitative intervention. A tumor may destroy normal structures, such as long bones or vertebral bodies. Pain from bone metastasis may represent impending or actual pathological fracture, which can affect a patient's function and rehabilitation by decreasing or inhibiting weight bearing on a limb or functional mobility when affecting the spine. The mass produced by a tumor may cause pressure effects, such as compression of neural structures resulting in focal neurological deficit. The neurological consequences of these pressure effects may be even more serious when the damage occurs within the bony confines of the cranium or spinal column. Hemiparesis from unilateral supratentorial lesions, paraparesis or quadriparesis from spinal (usually epidural) lesions, and incoordination or ataxia from cerebellar or brainstem lesions can all pose difficult rehabilitation issues. Similarly, lesions of the peripheral or central nervous system can cause disorders of speech or swallowing, which may require specific attention (3,4). More globally, central nervous system lesions that culminate in specific impairments of higher cerebral function (e.g., aphasia) or that produce overall cognitive impairment may complicate rehabilitative efforts at every level. Local pressure may also compromise vascular structures, producing limb edema; and in the case of lung lesions, local mass effect may decrease pulmonary capacity.

Direct effects of cancer	Treatments for malignancy
Indirect effects of cancer	Surgery
Paraneoplastic syndromes	Radiation therapy
Pain	Chemotherapy
Deconditioning	

TABLE 70-1. CAUSES OF FUNCTIONAL IMPAIRMENTS

Indirect effects of the neoplasm can also cause impairment. Pain may be quite debilitating, and general debility may have additional deleterious effects on function. Pain provoked by movement may produce functional weakness. Keeping the limb in a position that decreases pain may result in joint contracture (5). In populations with medical illness, musculoskeletal pains may result from the same pathologies that afflict those who are otherwise healthy, including myofascial pain syndromes, bursitis, tendinitis, or arthritis. At times, successful rehabilitation may help to diminish pain, as in the appropriate application of spinal bracing and improvement through a conditioning program.

Various paraneoplastic syndromes, such as the cancerrelated subtype of polymyositis-dermatomyositis, can produce weakness and also produce or worsen impairment (6,7). Impairments and disabilities also may result from sensorimotor paraneoplastic polyneuropathy, which is only one of a diverse group of paraneoplastic syndromes that may affect the neuromuscular junctions, dorsal root ganglia, or anterior horn cells (7,8,9 and 10). Paraneoplastic cerebellar degeneration may present with ataxia and dysarthria as the first evidence of a malignancy (11). Cancer-associated arthritis, which can complicate carcinoma, multiple myeloma, or leukemia, may resemble rheumatoid arthritis but may have asymmetric involvement, sparing the wrists and small joints (12,13). Hypertrophic osteoarthropathy, another paraneoplastic syndrome, may also cause polyarthritis as well as digital clubbing and periostitis. This is most commonly seen with bronchogenic carcinoma (14).

Most often, formal rehabilitation is requested to address impairments resulting from cancer treatment. Surgical resection of a tumor can produce varied impairments, depending on the tissues resected. Resection of lung tissue decreases pulmonary capacity. Creation of ostomies after gastrointestinal or genitourinary surgery requires instruction in their care and use. *En bloc* resection of lymphatic structures may give rise to lymphedema and focal muscle weakness may result from sacrifice of muscle tissue, as may occur in limb salvage procedures (15). Excision of bone for treatment of sarcoma may require placement of an endoprosthesis or amputation.

Surgery that injures nervous tissue often produces an obvious neurological deficit, and postoperative edema in the central nervous system may produce temporary deficits (16). For example, spinal accessory nerve palsy may arise after neck dissection for head and neck cancer or cervical lymph node biopsy (17,18 and 19). The patient may develop a depressed, protracted shoulder because of lack of trapezius upward rotation and retraction of the scapula. This results in impaired arm elevation.

Shoulder pain may arise when the upper limb is unsupported (20).

Radiation therapy may produce relatively acute effects, depending on the area irradiated. Chronic postradiation changes may evolve months or years later. The persistent impairments related to these effects may be profound.

Some chemotherapeutic agents have specific toxicities that affect target organ systems, such as the lungs or peripheral nervous system. Numerous chemotherapeutic agents cause polyneuropathy, with patterns that range from a presentation resembling Guillain-Barré syndrome (suramin) to sensory (cisplatin or paclitaxel) or sensorimotor (vincristine sulfate) neuropathy (21,22,23 and 24). Myopathy may result from corticosteroid use, with the predominate feature of proximal limb weakness (25). Avascular necrosis may occur from radiation therapy or corticosteroid use. All these measures may produce impairments that require rehabilitative intervention. Significant thrombocytopenia from chemotherapy may limit rehabilitation; “safe” platelet counts have not been precisely identified (26).

DECONDITIONING

Prolonged bed rest and immobility may produce a multitude of negative effects on various body systems. Muscle weakness and atrophy can result directly from immobility. As much as 20% of strength may be lost with each week of bed rest; endurance declines at a similar rate (27). The antigravity muscles of the trunk and lower limbs are often the first muscles to atrophy (28). Reconditioning often takes much longer than deconditioning. Strength increases approximately 12% per week until the muscle has threefourths of its maximal strength (29). Above this level, the rate of strength increase diminishes.

Muscles held in a fixed position gradually shorten, especially those that cross two joints. Patients undergoing prolonged bed rest maintain a position of comfort, often with the hips and knees flexed. This can result in contracture of the psoas and hamstring muscles. The gastrocnemius muscle often shortens as a result of positioning.

Prolonged bed rest may also result in osteopenia, which occurs when bone resorption exceeds bone formation (30). In severe cases, hypercalcemia may result and may worsen the hypercalcemia caused by bone metastases or other processes (31).

Cardiopulmonary deconditioning usually occurs with prolonged immobility. The resting heart rate can increase more than 30 beats per minute after only 2 weeks of bed rest (32). This is a compensatory means of maintaining cardiac output with decreasing stroke volume (31). Stroke volume decreases as immobilization diuresis leads to significant plasma volume loss (32,33 and 34). Postural hypotension may be another consequence of plasma loss. Although prolonged bed rest has no direct effect on pulmonary function, recumbency impedes diaphragmatic excursion, impairing cough (32,35). This may reduce tidal volume and cause compensatory tachypnea to sustain minute ventilation (33,35).

A hypercoagulable state related to malignancy combined with venous stasis from immobility places the cancer patient at high risk of deep vein thrombosis (DVT) (36). Remobilization of the patient with DVT may increase the risk of pulmonary embolus (37).

Prolonged pressure over bony prominences predisposes to pressure sores. Shearing forces, which are created when the patient slides or is dragged across the bed, may also compromise local blood flow and further increase the risk of pressure sores (38). Moisture from bodily fluids contributes to the formation of pressure sores by skin maceration and chemical irritation.

Finally, prolonged bed rest can lead to decreased gastrointestinal motility, which may predispose to constipation. Bowel dysmotility produced by immobility can augment the constipating effects of other disorders such as hypercalcemia, or treatments, including opioids.

THERAPEUTIC INTERVENTIONS

Rehabilitation interventions are best provided by a multidisciplinary team because of the diversity of functional impairments (Table 70-2).

Physiatrist	Psychiatrist
Physical therapist	Psychologist
Occupational therapist	Social worker
Speech pathologist	Clergy
Palliative care/pain specialist	Recreational therapist
Nurse specialist	Nutritionist

TABLE 70-2. MULTIDISCIPLINARY REHABILITATION TEAM

Rehabilitative interventions for the patient with progressive medical disease must be tailored to address the specific deficits of that patient (Table 70-3). Factors such as life expectancy, living environment, and the availability and capabilities of caregivers must be considered. Before a specific intervention is begun, the potential benefits to the overall quality of life of the patient must be weighed against the real costs in time, discomfort, and money as well as the potential physical, psychological, and psychosocial risks.

Therapeutic exercise	Physical modalities for pain relief
Mobility and gait training	Lymphedema treatment
Training in activities of daily living	Chest physical therapy
	Bowel and bladder retraining
Cognitive/perceptual rehabilitation	Speech and swallowing therapies
Orthotics and prosthetics	

TABLE 70-3. SPECTRUM OF REHABILITATIVE INTERVENTIONS

Therapeutic Exercise

Therapeutic exercise can help increase strength, endurance, range of motion, and coordination. It may significantly improve the patient's physical and psychological sense of wellbeing in a variety of settings (39). Cancer-related fatigue can be positively impacted by exercise (40,41). There is evidence that immunologic response can also be beneficially affected (42). Muscle can be strengthened through isometric, isotonic, or isokinetic exercises (43). Isometric exercise entails muscle contraction without joint movement. This form of exercise can be useful when pain is provoked by joint movement, such as in acute joint inflammation. Isometric exercise primarily affects strength and has little impact on endurance. Isotonic contraction produces joint movement against a constant force. Walking requires a series of isotonic contractions. Concentric isotonic contraction shortens muscle against constant resistance, whereas eccentric isotonic contraction partially counters a lengthening force on the muscle. This type of exercise helps to increase both strength and endurance. Isokinetic exercise is muscle contraction at a constant velocity and requires the

use of sophisticated, expensive equipment (44).

A typical reconditioning program for debilitated patients with progressive diseases features active range-of-motion exercises aimed at strengthening weak muscle groups (45). Exercises are generally done on an astolerated basis. Modifications may be necessary if precautions must be followed because of underlying organic conditions, such as metastatic bone disease or a recent myocutaneous flap. With significant weakness (less than antigravity strength), assisted active range-of-motion exercises may be needed. The therapist in part assists in moving the limb through its full range of motion. For patients with nonfixed joint immobility secondary to weakness, passive range-of-motion exercises performed by another person may be required.

In general conditioning exercises, low-resistance, highrepetition exercise is used to increase endurance (46). An elastic band may be used to strengthen muscle by providing low to moderate resistance. Patients who are isolated for medical reasons and are unable to walk for endurance training may benefit from the use of bicycle pedals. If feasible, a progressive resistance exercise program is initiated to further strengthen muscle (47).

Range-of-motion and strengthening exercises and compensatory techniques to achieve movement using less affected muscle groups are used in therapy for spastic hemiparesis. Neuromuscular reeducation techniques may facilitate or inhibit spastic synergistic patterns, eventually promoting isolated muscle movement. Neuromuscular reeducation may be facilitated by the use of electromyographic biofeedback or functional electrical stimulation (FES) (48,49 and 50). For example, FES may improve movement and position of the hemiparetic shoulder (51). If needed, arm positioning is further assisted through the use of a sling during ambulation. In the seated or bedbound patient, the sling should be removed and replaced by other supportive devices, such as a lap board or arm trough (52). The paraparetic and quadriparetic patient may benefit from neuromuscular reeducation and sustained muscle stretching. There is evidence that acupuncture and electroacupuncture can result in improved neurological and functional outcomes in hemiparetic stroke patients (53). Spasticity also may be decreased by physical modalities such as transcutaneous electrical nerve stimulation, ice, electromyographic biofeedback, and FES (54,55,56 and 57). Baclofen, administered orally or intrathecally, is an effective antispasticity agent when physical modalities are not helpful (58). The negative effect of losing what was functional spasticity—for example, quadriceps spasticity maintaining knee extension— must be balanced against the positive effect of increased mobility. When spasticity of an isolated motor group interferes with function, chemical or surgical neurolysis, motor point block, or tenotomy may be considered (57).

When nerve injury or muscle sacrifice has occurred, the goal of physical intervention is to increase active, functional movement. Exercise and FES may be aimed at increasing the strength of the partially sacrificed or partially denervated muscle. Other muscles are strengthened to compensate for the acquired weakness, and instruction in postural and compensatory techniques is given.

In cerebellar disorders, patients lose the smooth coordination of agonist and antagonist motor groups (59). Such incoordination produces intention tremor, ataxia of the limbs, and disturbance of fine and rapid alternating movement. The use of weighted equipment may help decrease tremor amplitude and increase function.

In selected patients, cardiovascular reconditioning may be hastened by appropriate therapeutic exercise. The first aerobic exercises usually recommended are walking or wheelchair mobility. To achieve aerobic benefit, these exercises should be performed for at least 15 minutes, 3 days per week (60). The physical or occupational therapist may use heart and respiratory rate, blood pressure determination, and pulse oximetry to monitor the patient's cardiopulmonary status.

Joint contractures may arise from prolonged immobilization, muscular imbalance, voluntary immobility to maintain a position of comfort, malignant invasion of joint or adjacent soft tissues, or high-dose radiation therapy to the joint (5,61). Prevention of contractures is easier than treatment. Once contractures develop, aggressive intervention is required when it is feasible. Range-of-motion exercises with sustained terminal stretch may be effective, especially in mild myogenic contractures (62). When not contraindicated, deep heating of tissue may increase the distensibility of collagen and assist in reducing contracture (63). With severe contracture, dynamic splinting or serial casting may be beneficial (64).

In the lower-limb amputee, lying in bed or prolonged sitting can encourage hip and knee flexion contracture. These contractures may not be prevented by ambulation without full joint extension. Lying prone at regular intervals daily may help prevent hip contractures.

Mobility and Gait Training

Early mobilization may help improve recovery after certain interventions, such as laparoscopic colonic resection (65). Patients with severe debility may benefit from mobility instruction. This begins with bed mobility, such as scooting, rolling, and sitting up; these actions may prevent some of the deleterious effects of bed rest, such as pressure sores. Patients who cannot tolerate upright positions because of orthostatic changes may require progressive upright tolerance training. The hospital bed can be used initially for this training. The patient may next begin sitting with the legs dangling. At times, the seated position cannot be tolerated. A tilt table may be used to gradually incline the patient from a supine position toward a standing position (45). Along with sitting and standing postures, instruction in static and dynamic balance in these positions may be necessary.

A transfer is defined as movement from one surface to another. The most common transfer is a standing transfer, for example, going from a bed to a chair. If patients are unable to transfer, they may require the assistance of another person or the use of an assistive device, such as a walker or sliding board (66). Some patients may require instruction for transfers directly into a chair or wheelchair. Those requiring a wheelchair usually are trained in transfers from a wheelchair to another seating device, such as a commode or car seat (67).

Early progressive ambulation can help prevent the negative effects of deconditioning. A walker or another assistive device may be required. Ambulation training may be facilitated by parallel bars or with support from a rolling pole or wheelchair. These assistive devices widen the base of support and involve the upper limbs in weight bearing (68).

Cerebellar gait ataxia may be associated with limb or truncal incoordination (59). In an effort to decrease the amplitude of the tremor, a weighted walker or limb weights may be beneficial, and other adaptive equipment may also be weighted (69). In some patients, ataxia cannot be improved through rehabilitative interventions.

The pathophysiology of sensory gait ataxia is proprioceptive loss in the lower limbs. The use of an assistive device allows proprioceptive feedback to one or both arms. Impaired joint position sense also may be partially compensated by attention to visual cues. Environmental adaptations should include adequate lighting and unobstructed walkways (70).

The spastic hemiplegic gait often features an extensor synergy pattern in the affected lower limb. The foot and ankle assume an equinovarus posture, with the knee held in extension. The patient may circumduct the affected leg, raise the hip, or lean away from the affected leg to permit foot clearance during the swing phase of gait (71). The use of an ankle foot orthosis (AFO) can assist in foot clearance. A double metal upright AFO may be attached to an orthopedic shoe; a calf band with Velcro closure is attached to the superior portion of the metal uprights. More often, a custom-molded plastic AFO is prescribed. This AFO extends from the plantar surface of the foot up the posterior aspect of the calf and is secured to the leg by a Velcro closure. Compared with the metal AFO, the plastic AFO is lighter in weight, has a larger area of contact, and offers a better cosmetic appearance. Either AFO may improve speed and decrease energy expenditure, but neither has a significant advantage over the other (72).

Lower limb weakness without spasticity may benefit from different compensatory techniques. Hip extension may be able to compensate for weak knee extensors (73). The knee may also be forcibly extended by the hand pushing backward on the thigh. In either case, genu recurvatum may be the undesirable result. Knee bracing may be required if knee instability persists despite efforts to compensate for the weakness. For example, this may occur after some limb salvage procedures. Bracing cannot effectively compensate for profound hip flexor or extensor weakness (52). Conversely, weakness localized to all or part of the distribution of the common peroneal nerve may be compensated for with an AFO. This prevents plantar flexion during the swing phase of gait and lessens the risk of falls associated with foot drop. With the use of effective leg braces, other assistive devices may not be needed.

Activities of Daily Living

ADLs include dressing, eating, bathing, and writing (74). Coordination and strength training in combination with ADL instruction may be needed for bilateral upper limb weakness. If one or both upper limbs are weak, adaptive equipment may be required for ADLs (75). The use of a rocker knife may assist in one-handed food cutting. Widehandled utensils, along with fine motor retraining, may be helpful for patients with distal upper limb weakness. Patients with severe, long-term dominant limb weakness may require dominance retraining for many of their ADLs. Bimanual activities should be encouraged in these patients. However, some have advocated constraint-induced movement therapy, in which the unaffected arm is constrained within a sling most of the waking time of the patient, for hemiparesis after stroke and traumatic brain injury. The hemiparetic limb with some residual function may make significant functional gains with intensive training (76). However, this remains controversial. A long-handled shoe horn and a reacher may help in dressing the lower extremities. Other adaptive equipment may be necessary in the wheelchair-dependent patient, such as a raised toilet seat, a tub chair, and various other environmental adaptations. ADL assessment may be of some help even in estimation of length of survival in terminal patients (77).

Cognitive/Perceptual Rehabilitation

Cognitive/perceptual rehabilitation helps improve or maintain the patient's level of daily function, especially with ADLs and social interaction. Simple techniques, such as the use of a notebook, may be helpful memory aids. The adverse impact of unilateral visual field deficit or neglect may be reduced in part by various occupational therapy exercises, some facilitated by computers. Other specific problems may also be helped by tailored strategies, which then require repetitive application.

Braces and Splints

An orthosis is a device that provides support to a body part and may assist in the function of that part. Orthoses may be used to support fractured long bones or a limb that is paretic or plegic. Functional splinting may be used when some volitional movement remains in the afflicted limb.

Upper extremity bracing includes the resting hand splint used for the spastically flexed hand and the cock-up wrist splint. The cock-up splint places the wrist in mild extension, enhancing hand function by placing the finger flexors in a mechanically advantageous position. Lower limb orthoses include the different AFOs and knee braces.

Spinal orthoses are used to add support to sections of the spine. They are especially useful to decrease pain provoked by movement of the afflicted area. These orthoses help prevent movements, especially forward flexion in the thoracic and lumbar spine, that place additional stress on vertebral bodies compromised by bone disease. Both abdominal binders and lumbosacral corsets provide some support to the spine by increasing intraabdominal pressure. For greater restriction of movement, lumbosacral or thoracolumbosacral orthoses may be prefabricated or custom-made as body jackets (78,79). All spinal orthoses must be used in a manner that avoids direct pressure over ostomy sites, hopefully without compromising the support provided by the orthosis. Patients with pulmonary compromise must be carefully assessed to avoid respiratory compromise caused by lumbar orthoses that increase intraabdominal pressure. Skin lesions may need to be accommodated by relief of pressure directly over the lesion.

Bracing of the cervical spine can provide the greatest restriction of movement (80). A soft cervical collar serves as a reminder, only minimally restricting movement. A more rigid device, such as a Philadelphia or Miami collar, provides some restriction, especially of flexion and extension. More limitation of movement is provided by a four-poster appliance or a sterno-occipito-mandibular immobilizer. More complete immobilization is achieved by a halo vest.

Prostheses

Sacrifice of the distal portion of a limb may require the use of a functional prosthesis. In the lower limb, the goal is a return to independent ambulation. The more proximal the level of amputation, the greater the increase in energy expenditure for reciprocal gait. The exertion required may preclude the use of prostheses by patients with comorbid cardiopulmonary disorders. Lighter-weight components, improved socket designs, and energy-storing feet whose elasticity allows some energy to be released during toe-off have improved modernday prostheses (81,82 and 83). In all cases, proper care of the distal residual limb and appropriate prosthetic training are required for maximal benefit to be achieved.

Upper limb amputation is much less common. A typical upper limb prosthesis has a socket that serves as an interface between the prosthesis and the residual limb. The most important functional component is the terminal device, which is available in different shapes (including a functional hand). Control of the terminal device may be achieved mechanically by shoulder movement. After forequarter amputation, a shoulder prosthesis may allow more normal fit of clothing. All prostheses, especially the expensive myoelectric ones, may be impractical for use in populations with advanced disease.

Physical Approaches to Pain Relief

Physical therapeutic modalities may be helpful in the cancer patient with pain of muscular origin (84). Both cold and heat have direct effects on local muscle spasm and can provide analgesia. Heat can increase local blood flow and metabolic rate and therefore is contraindicated in the cancer patient whose pain is at the site of a tumor mass. This is especially true with deep heating devices, such as ultrasound diathermy (85). These and other modalities, such as vigorous electrical stimulation and massage, are avoided in areas of active tumor growth and over irradiated tissues.

Therapeutic cold causes an initial decrease in temperature through vasoconstriction. Like superficial heat, cold may also be a counterstimulant, tending to inhibit the projection of pain information in the central nervous system. It, too, should be avoided over irradiated tissues (86).

Electrical stimulation, which may also have a counterstimulating effect, is usually applied superficially for pain via transcutaneous electrical nerve stimulation. If pain is strictly of myogenic origin, electrical current also may be used to fatigue muscle spasm or relieve muscular tightness from myofascial trigger points (87). Ischemic compression (pressure maintained over a trigger point) or the spray and stretch technique (vapocoolant spray followed by muscle stretch) may also be effective in releasing trigger points. When these methods are insufficient, injection of trigger points with local anesthetic, or dry needling, may be helpful. Acupuncture has also been useful in a number of musculoskeletal pain complaints (88). Whatever method is used, reconditioning of the muscle containing the trigger point is required. Therapeutic exercise should be aimed at recovering full range of movement and strength of involved muscles, as well as fostering improved posture and body mechanics. Recreational therapy may also play a role in pain management, even in hospice care (89).

Evaluation of the effective uses of different modalities in treating pain relies heavily on ratings of pain intensity by the patient. Certainly, aspects of physical or occupational therapy requiring movement may exacerbate or bring on pain. Therapy should be modified as needed. When getting ratings from the patient, it must be remembered to differentiate pain intensity from pain affect, and that recall of both in the past is positively correlated with current levels of perceived pain (90).

Treatment of Limb Swelling

DVT is a common problem in the cancer patient, especially in those who are bedridden. In addition to pharmacological measures, several mechanical methods have been used for prophylaxis of DVT (91,92,93 and 94). These measures include intermittent pneumatic pressure pumping, gradient pressure stockings, and electrical stimulation of calf muscles.

Controversy exists concerning the timing of mobilization of the patient with DVT. Early mobilization may place the patient at risk of embolization, but prolonged bed rest may increase venous stasis and encourage clot formation. The decision when to mobilize the patient is based in part on the location of the lesion, the length of time the patient has undergone anticoagulant therapy, and whether an inferior vena cava filter has been placed (95,96).

Lymphedema is a frequent cause of limb swelling in the cancer patient. Even when mild, lymphedema can produce profound psychological effects in the patient, in addition to physical sequelae (97,98). When lymphedema is soft and pitting, limb elevation may be helpful. Physical treatment, which has its foundation in the use of static compression garments, may be helpful even when the condition is mild. Most frequently employed are gradient pressure elastic sleeves or stockings. Bandaging techniques, using materials with little compliance, are also used, and a legging orthosis made of noncompliant Velcro straps has been helpful in certain instances (99,100). Static compression facilitates the muscle pump action of muscle contraction. Thus, therapeutic exercise in the affected limb should be performed while the patient is wearing the compression garment.

For more significant lymphedema, a pneumatic compression pump may be used, although its use is increasingly controversial. Compression is usually applied in a distal-to-proximal direction via an overlying sleeve covering the entire limb (101,102). The intent is to pump fluids out of the limb, but the concern is the lack of a means of egress for the fluid when lymphatic drainage is insufficient.

A combination of physical therapies featuring manual lymphedema treatment (MLT) is another approach that attempts to facilitate flow through residual patent lymphatic channels (99). In principle, MLT helps to enhance lymph drainage from one area of the torso to another. For example, if lymphedema after axillary lymph node dissection is secondary to impaired lymph drainage from both the ipsilateral limb and the upper quadrant of the torso, MLT attempts to enhance lymph flow from the affected upper quadrant to other areas of the torso via the collateral lymph channels. Bandaging the limb between MLT sessions helps to maximize treatment results (103). One study, however, suggested that adding MLT to bandaging, exercise, and education may not significantly further improve edema reduction (104). Active disease is a relative contraindication to any of these dynamic treatments, as may be local infection, congestive heart failure, or acute DVT (99). With severe lymphedema, some have suggested lymphaticovenular anastomosis in addition to postoperative bandaging (105).

Chest Physical Therapy

Chest physical therapy assists in mobilizing secretions and enhancing gas exchange in the lungs. Patients who are immobilized in bed should be repositioned every 2

hours (106). This may prevent pooling of secretions in the dependent portions of the lungs. The therapist can administer postural drainage to help remove secretions from specific areas of the lungs (107). Chest vibration or percussion is often used in combination with postural drainage to enhance its effect. A nebulizer may be used before chest physical therapy to loosen secretions and deliver a bronchodilator. In selected cases, muscles of ventilation are subjected to specific reconditioning exercises (108). The use of an incentive spirometer between therapy sessions may strengthen the muscles of respiration and help prevent arteriovenous shunting (107). Weekly counseling with breath retraining and relaxation exercises may improve distress from breathlessness in patients with lung cancer (109).

Bladder and Bowel Retraining

Bladder incontinence in the cancer patient is usually managed initially with Foley catheterization, either urethral or suprapubic. If practical, intermittent catheterization is preferred because of the decreased risk of bacteriuria and formation of bladder stones (110). Elevated intravesicular pressures can occur in neurogenic bladders with detrusorsphincter dyssynergia; this may be avoided with appropriate timing of clean intermittent catheterization. Condom catheters are an alternative in the male patient when this increased intravesicular pressure is not a problem (111).

In the patient with spinal cord disease, especially above T6, autonomic dysreflexia may be provoked by noxious stimuli below the level of injury. For example, bladder distention caused by indwelling catheter obstruction may cause headache, flushing, and sweating above the level of injury, as well as hypertension accompanied by bradycardia (112,113). Interventions for autonomic dysreflexia include correction of noxious stimuli and symptomatic therapies, such as elevation of the head of the bed or the use of antihypertensive medications if necessary.

Bladder incontinence may also be treated with drugs. For example, decreased bladder wall contractility in the spastic, reflex bladder may be achieved with anticholinergic agents. Conversely, cholinergic agents, which may increase bladder contractility, should be used cautiously.

A patient with an uninhibited bladder may require a scheduled voiding regimen. Timed voiding combined with such measures as the Valsalva maneuver, suprapubic tapping, and suprapubic pressure (Credé) may be particularly useful when mild urinary retention is present.

Constipation due to bowel dysmotility is a common problem in the medically ill. Many patients find that bowel movements are facilitated by the upright seated position, and this may be an important goal of rehabilitation. Increased mobilization enhances bowel motility and may be a part of a multimodal strategy for constipation, which commonly includes increased fluid intake, fiber consumption, and laxatives (114). Patients with neurogenic bowel due to a lesion of the spinal cord, cauda equina, or pelvic nerves may benefit from other techniques, such as stimulation of anorectal mucosa and the use of either suppositories or digital stimulation (115,116). With fecal impaction, digital extraction may be necessary (117).

Management of ostomies includes dietary manipulation, control of fluid intake, drug therapies (laxatives or constipating drugs), and appropriate local stoma care. The goal of appropriate care is to produce a controlled effluent and to minimize odor and soiling. A pouch may be worn to prevent soiling of clothes and to collect feces and urine. These patients should avoid wearing constrictive clothing.

Swallowing and Speech Therapies

The stages of swallowing are the oral phase, the pharyngeal phase, and the esophageal phase, each of which is defined by where the bolus of food is located. A swallowing disorder can arise from neurological dysfunction or a structural lesion that causes problems with any or all of these stages. A variety of rehabilitative approaches can be used to cope with dysphagia (118,119 and 120). The risk of aspiration may be lessened by different textures of food or liquids and by head and body positioning (e.g., a chin tuck) that help protect the airway.

The manner of oral intake also may be modified to reduce the risk of aspiration. In the supraglottic swallow, the patient holds the breath before and during the swallow and coughs at its completion, decreasing risk of aspiration. The use of a smaller bolus of food or multiple swallows per bolus can help clear the pharyngeal area. Vocal cord adduction exercises may be performed to improve airway closure and protection. Prosthodontic appliances may be required for patients who have undergone resection of part of the oral swallowing mechanism. For example, a palatal augmentation prosthesis adds bulk to the hard palate, which may enhance tongue-to-hard-palate contact after partial glossectomy (121).

Rehabilitative techniques may be used to address disorders of language. Language abilities may be improved by melodic intonation therapy and alternative communication techniques. In melodic intonation therapy, the patient produces verbal communication within the framework of a familiar tune to facilitate word production (122). Alternative communication techniques comprise a variety of nonverbal methods, such as a communication board with pictures, letters, or words.

Dysarthria may arise from neurological insult or structural damage. Patients with hypernasal speech may benefit from a palatal lift, which decreases nasal air emission. A palatal obturator may be used to fill a surgical defect of the hard palate. Techniques of pausing or rate control may be used to maximize speech production (123). Vocal cord adduction exercises may improve dysphonia after unilateral vocal cord paralysis.

Patients who undergo laryngectomy or tracheostomy may be aphonic or dysphonic. Several methods of voice production are available. An electrolarynx creates vibrations, which can be transmitted to the oral cavity either via an oral tube or by transmission through soft tissue when placed on the neck (124). Tracheoesophageal puncture uses a small voice prosthesis inserted into a fistula between the trachea and esophagus (125,126). The patient may also be instructed in esophageal speech (127). In all cases, extensive speech therapy is required for proper training.

BENEFITS OF REHABILITATION

Traditional Settings and Palliative Care

Rehabilitation interventions can play an important role for the patient with cancer in a variety of settings. Functional impairments often result from prolonged bed rest and the resulting deconditioning. This is frequently seen in combination with neurological loss (128). Chronic impairments that undermine quality of life are often addressed by palliative care specialists. Although pain is most frequently the reason for referral, many other symptoms warrant intervention. Rehabilitation referral is certainly appropriate when motor, sensory, or cognitive function is impaired, as well as those related to persistent pain. Its role is at times overlooked or underused even when patients are receiving intensive palliative care. Interventions can be arranged for the patient admitted to the oncology service depending on the impairments and any contraindications to therapy (129). Therapies may be delivered at bedside or in the rehabilitation department.

When the patient will benefit from more intensive rehabilitation, transfer to an inpatient rehabilitation service is of potential benefit, if the patient is medically stable. The full spectrum of specialists are then available to the patient, and physical and occupational therapists work with the patient each day. The patient's ability to participate at this more intense level is usually a prerequisite to admission. Many cancer-related impairments are quite similar to those more traditionally thought of as rehabilitation candidates. For example, those with central nervous system malignancy may have clinical manifestations of spinal or brain pathology that mirror those seen in spinal cord injury, traumatic brain injury, or stroke. It should be recognized that inpatient rehabilitation can help improve both motor and cognitive function in some patients whose impairment is malignancy- or treatment-related (130). Huang et al. found that those with brain tumor achieve similar functional outcome with shorter lengths of stay in the inpatient rehabilitation service than those with brain injury (131).

If the patient is discharged home from the medical, surgical, or rehabilitation service, therapy can be continued at home through the appropriate home services agency. If the patient is able to be transported and would benefit from a formal rehabilitation clinical setting, outpatient therapy can be arranged. Rehabilitation services are also available in most nursing homes and skilled nursing facilities.

Hospice Settings

For those with advanced disease and a life expectancy generally of less than 6 months, hospice care may be the most appropriate option. Such programs provide inpatient or home-based comprehensive care for the dying patient. Comfort care is emphasized, forgoing any concentration on curative therapies (132). An interdisciplinary hospice team may include physical and occupational therapists, but a physiatrist is involved only as a consultant in most programs. The team should regard the patient along with his family and close friends as the unit requiring care, and professional friendship and “gentle openness” are required of the team (133) (Table 70-4).

Physician	Occupational therapist
Nurse	Counselor
Social worker	Chaplain
Physical therapist	Nutritionist

From Lynn J. Serving patients who may die soon and their families. The role of hospice and other services. *JAMA* 2001;285(7):925, with permission.

TABLE 70-4. MEMBERS OF THE HOSPICE INTERDISCIPLINARY TEAM

Patients admitted to an inpatient hospice setting are often highly dependent and have major functional impairments. In one survey, fewer than 17% of patients could walk unassisted and only slightly more than 20% were chairbound; the rest were bedbound (134). A retrospective study found that surviving family members of deceased hospice patients reported that almost 90% of patients wanted to walk or use a wheelchair, almost 80% were satisfied with rehabilitation efforts, and more than 60% felt rehabilitation procedures had been effective (135). In general, inpatients in a hospice spend more time with their families and are more satisfied with their care than those receiving more conventional care (136,137).

The role of the physical therapist in the hospice setting is somewhat modified. The physical therapist must attend to the physical function of the patient and help maintain function as long as possible. The therapist must also attend to nonphysical aspects of care to possibly foster social cohesion, define meaningful physical activities, and help support the patient's confrontation with the issue of mortality (138). It is important for the therapist to be an active listener and problem solver, and to help reduce the burden for the caregivers (139). Similarly, the occupational therapist should help the hospice patient identify and carry out meaningful activities, including socialization with others (140). They may also help the team identify impairments in communication, which may be more prevalent than suspected (141).

CONCLUSION

Rehabilitation interventions can have a tremendously positive impact on the patient's quality of life. Even in those with a short life expectancy, functional improvements and pain reduction may benefit the patient's family and other caregivers. Interestingly, families that participate in the patient's rehabilitation feel it is more effective and satisfactory to the patient than those families that do not participate at all (135). Rehabilitation can also help the patient be more capable of putting personal and social affairs in order at the end of life.

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71

REHABILITATION OF SPEECH DISORDERS

STEVEN B. LEDER

Communication, especially verbal communication, receives very little attention in everyday life. Why should attention be directed at something everyone does with such ease? All human societies, in fact, have used speech and have found it to be the most convenient form of communication (1). Most people rarely think, however, about not being able to speak, or suddenly having a speech mechanism that does not function as efficiently as it used to, or not being able to hear as well as they did. This, unfortunately, is exactly what happens when a surgical resection involves the structures of the mouth or larynx, a tracheotomy is performed for airway maintenance, or chemotherapy or external beam radiation therapy (EBRT) affects auditory acuity.

Speech communication is far more than just the obvious movement of lips and tongue. It is a highly complex phenomenon that takes place between a speaker and listener. It encompasses linguistic encoding and decoding (the message), physiological commands (neural and muscle activity), and acoustic features (the sound wave). Overlaid on this system is individual speaker variability, i.e., different people do not produce the same sound waves when pronouncing the same word. In fact, the same speaker does not even produce identical sound waves when pronouncing the same word on different occasions.

How, then, is speech understood? The listener does not rely solely on information from the acoustic features in the sound wave. Knowledge of the rules specific to a particular language and speech system, cues provided by context, and the identity of the speaker are all used to decode the speech signal. Speech communication, therefore, relies on a great number of ambiguous and, most importantly, redundant cues, not on a precise knowledge of a limited number of specific cues (1). This is the only way millions of different speakers producing many millions of different sound waves can be understood by millions of different listeners.

Communication is the essence of a person's personality and social identity (2). The goal of all communication rehabilitation after cancer treatment is to reinstate verbal communication as well as possible so the person can be accepted and not stigmatized by society. Speaking, rather than nonverbal communication (lipreading, communication boards, writing or typing, or computerized augmentative communication systems) is the preferred mode for receptive and expressive communication. Speaking is accepted best by the individual and family, is the most efficient and easiest to use (when possible), and maintains a familiar link with the pretreatment life with which the individual was familiar.

Meaningful and understandable communication is greatly needed after a diagnosis of cancer. Communication is critical to a patient's medical care, psychological functioning, and social interactions (3,4). When communication breaks down between the patient and health care professionals, the patient's ability to participate meaningfully in the health care plan is greatly restricted (5,6), and recovery and rehabilitation may be adversely affected (2).

This chapter discusses the ways cancer and its treatment affect the individual's ability to maintain verbal communication skills. It also discusses extensive rehabilitation methods whose goal is to reinstate verbal communication skills for the individual. In addition, the chapter considers the importance of hearing, its potential loss after cancer therapy, and rehabilitation strategies with the goal of maintaining optimal verbal communication.

PRODUCTION AND PERCEPTION OF SPEECH

Speech, swallowing, and breathing are different types of behaviors that share the same anatomical structures. Swallowing and breathing are very old evolutionary behaviors and occur in all animals. Speech is a recent evolutionary behavior and occurs only in humans (7). The shared anatomical structures that move and are involved in speech production are called the articulators: the lips, tongue, teeth, mandible, velum, pharynx, and larynx. Other shared anatomical structures are the oral and nasal cavities, which provide resonance, and the lungs and diaphragm, which provide the air supply and driving force without which normal speech would be impossible. Although the exact neural. controls for speech production are not known, the neural controls for swallowing and speech also overlap, and the reader is referred to Chapter 12, Dysphagia, for a more detailed discussion of the neural innervation of shared structures.

Speaking is a highly complex motor skill that consists of coordinated movements of the articulators—the lips, tongue, and teeth—on the air generated from the lungs (cf. 7–14 for a more detailed discussion of speech production and perception). With reference to speech, the vocal tract is defined by the larynx inferiorly and includes the pharynx, oral cavity, and nasal cavity superiorly. Any mass change (as with a tumor) or insult (as with a surgical resection or denervation) to the vocal tract or articulators may affect voice production (the sound source, voice quality, and resonance) and speech production (consonant and vowel articulation). Depending on the cancer treatment required, the person's ability to communicate verbally is affected mildly to severely to totally.

The speech-language pathologist's role is to diagnose the communication disorder and provide optimal rehabilitation after treatment, with the goal of having the patient acquire verbal communication skills that are as nearly normal as possible. Realistic goals, sometimes requiring interim steps, are presented to the patient. Success at each step is stressed to help the patient stay motivated and to help prevent depression. All types of communication, such as writing or lipreading, are used initially so as to connect the patient to the environment and foster participation in the rehabilitation plan as quickly as possible.

CLINICAL APPLICATIONS

Head and Neck Cancer Resections and Reconstructions

The results of surgery and reconstruction vary as they affect and change speech production skills, verbal communication, and speech perception acceptability, but they affect all cases to some degree. A database has been designed to evaluate functional outcomes of speech, swallowing, and voice after head and neck cancer treatment, and longitudinal data is currently being collected (15).

It should be kept in mind that as long as the intended target phoneme (consonant or vowel) is articulated with enough acoustic and distinctive features to be considered

an allophone of the target phoneme, the meaning of the word is not changed, and the verbal message is considered to be encoded and decoded successfully. Ideally, the surgical resection and reconstruction (with or without postoperative chemoradiation) coupled with appropriate rehabilitation allows for intelligible verbal communication by maintaining at least the minimal redundant cues in the speech signal needed for successful verbal communication. For example, it was reported that pre-/postoperative speech function did not differ in small oral and base of tongue resections when primary closure versus flaps were compared (16) and in irradiated versus nonirradiated postsurgical oral cancer patients (17).

Unsuccessful verbal communication, however, results when the surgical resection has altered the vocal tract or articulators to such a degree that the inherent redundancy built into the speech code becomes degraded. As a result, the target phoneme is decoded not as an allophone but either as a different phoneme (thus changing the meaning of the intended message) or as an unintelligible sound not considered part of the phonology of the target language, in this case English.

Counseling

Nothing can fully prepare the patient for the consequences of head and neck cancer surgery. Combined with the emotion and fear inherent in the word “cancer” is the fear of major surgery and its consequences, the fear of losing the ability to communicate effectively, and the fear of becoming a social and psychological burden on the family. An indepth discussion of the need for counseling, both preoperatively and postoperatively in the long term, appears in reference 2.

The speech-language pathologist offers preoperative counseling to discuss the surgery and its consequences and, just as importantly, the rehabilitation strategies that are used to restore verbal communication skills to as nearly normal a state as possible. Illustrations and models are helpful in having the individual understand what impact the planned surgery may have on the speech-production mechanism.

Counseling does not begin and end preoperatively. The immediate postoperative period of 1–14 days presents problems that are not encountered later on. Postoperative edema impairs articulation, and the patient should be reassured that this is a temporary condition. Sutures are frequently present, and localized pain may also reduce the proficiency of articulation. If the facial (C-VII), vagus (C-X), or glossopharyngeal (C-XII) nerves were involved in the surgical resection, paresis or numbness may be present, further impairing articulatory precision. Also, the patient's decreased motivation and sadness may make speech production worse in the immediate postoperative period than it will be in a few weeks' time. Counseling should continue postoperatively for as long as the patient needs it (2).

After the 2-week postoperative period, the patient is usually discharged home. Before discharge, the speechlanguage pathologist determines whether ongoing speech rehabilitation is required. If it is, additional goals are implemented to increase overall speech production skills and the intelligibility of speech, based on the surgical resections and the functioning of the remaining structures in the vocal tract. The patient is assured that articulation and speech intelligibility will improve with therapy. If there is a structural defect that can be compensated for with, for example, a palatal prosthesis, an appropriate referral to a prosthodontist is done as well.

Speech Articulation Rehabilitation

The ultimate goal of rehabilitation is to return the patient to as nearly normal a life as possible, regardless of the amount of time that remains. Speech articulation rehabilitation after resection of the articulators and vocal tract focuses on compensatory articulation and stresses precise articulation. The goal of speech articulation therapy is to produce either the target phoneme or an allophone of the target phoneme so the word, and therefore the message, is decoded correctly by the listener.

Labial Resections

Labial resection can result in decreased lip rounding, affecting vowel production (e.g., /u/), and labial closure, affecting articulation of bilabial /b,p,m,w/ and labiodental /f,v/ consonants.

Anterior Tongue and Floor of Mouth Resections

Resection of the anterior tongue and floor of the mouth can result in decreased lingua-alveolar ridge contact, affecting the production of all consonants with the /t,d,s,z,n,l/ place of articulation, as well as the linguadental phoneme /th/. The manner of articulation of these phonemes can also be impaired because of poor lingua-alveolar ridge contact. For example, inadequate lingua-alveolar pressure for the stop plosive phoneme /d/ results in articulation of an /n/ or /l/ phoneme.

Lateral Tongue Resection

Because of the redundancy built into the speech production mechanism and the decoding ability of the human brain, lateral tongue resections do not usually result in significant articulation errors that impair speech intelligibility. The remaining hemitongue is able to articulate allophones of the target phoneme. Lateral emission of air may occur after more extensive resection, especially if teeth are missing as well.

Posterior Composite Resections

Posterior composite resections affecting more than one structure, such as the tongue and the mandible, can result in decreased lingual and mandibular range of motion and control, paresis, and decreased sensation, which in turn can affect vocal tract shape for vowels, and place and manner of articulation for consonants, especially the velar phonemes /k,g/.

Hard and Soft Palate Resections

Hard and soft palate resection affects velopharyngeal closure, resulting in velopharyngeal insufficiency or oronasal fistulas. These defects may cause excessive hypernasal resonance because of the inability to separate the oral from the nasal cavities. The larger the surgical defect, the greater the inappropriate hypernasal resonance. All phonemes are affected, with stop plosive, fricative, and affricate phonemes—the pressure consonants—affected the most because of the inability to build up adequate intraoral air pressure for their articulation. For example, without adequate intraoral air pressure for the release burst, the stop plosive phonemes /p,b/ are articulated and perceived as the phoneme /m/, significantly impairing speech intelligibility.

Partial Laryngectomy

There are several different types of partial laryngectomies (2). The following are done in the vertical plane: cordectomy via laryngofissure (18), hemilaryngectomy (19), vertical partial laryngectomy (20), anterofrontal and extended anterofrontal laryngectomy (18), and near-total laryngectomy (21,22). Voice production and voice quality after these operations is dependent on the extent of the laryngeal resection and the type of neoglottic reconstruction used (19). Therefore, this population demonstrates a range of vocal capabilities (23).

In general, partial laryngectomy results in hoarseness and possibly breathiness because of the resection, which usually includes one arytenoid cartilage and one true vocal fold, and reconstruction of the neoglottis with mucosa opposing the remaining true vocal fold. The resultant novel vibration of the remaining true vocal fold against mucosa results in a turbulent sound source, changing vocal tract resonance patterns and producing the voice disorder.

Supraglottic Laryngectomy

The surgical procedure for a supraglottic laryngectomy is done in the horizontal plane. Candidates for a supraglottic laryngectomy are those with cancer of the epiglottis or ventricular vocal fold(s) without cancer extension across or into the ventricle or anterior commissure (18).

Supraglottic laryngectomy does not affect articulation or true vocal fold vibration, but may affect vocal tract resonance and voice quality because it alters the physical characteristics of the vocal tract. Specifically, the removal of the epiglottis, aryepiglottic folds, and false vocal folds in the pharynx alters the length and volume of the vocal tract and may change the resonant characteristics of the vocal tract. Information in this area is scarce. In one of the few studies reporting objective data on the phonatory results after supracricoid partial laryngectomy (24), it was found that the average fundamental frequency for the partial laryngectomy subjects was not significantly different from that for normal speakers. Additional data indicated that partial laryngectomy speech and voice production was less efficient than normal speech and voice production as evidenced by increased jitter, shimmer, and harmonics to noise ratio, and decreased maximum phonation time, speech rate, and phrase grouping.

Metal and Plastic Tracheotomy Tubes

The most disruptive change for the posttracheotomized patient is the loss of verbal communication (25,26 and 27). There are two major types of tracheotomy tubes: metal (stainless steel) and plastic. A metal (Jackson) tracheotomy tube is always cuffless. Inspiration occurs through the tube. Expiration occurs out of the tube when it is open and via the upper airway and out of the mouth and nose when the tube is occluded (Fig. 71-1). Plastic tracheotomy tubes can be either cuffed or cuffless. The cuff is an inflatable diaphragm attached around the distal end of the tube. When the cuff is inflated, expiration occurs out of the tube, and when the cuff is deflated and the tracheotomy tube occluded, expiration must occur via the upper airway and out of the mouth and nose (Fig. 71-2). Both types of tracheotomy tubes have inner cannulas whose purpose is to facilitate maintaining hygiene and the patency of the tube itself (Fig. 71-1 and Fig. 71-2). In addition, both types of tubes can be fenestrated, i.e., by a hole or holes placed on the superior surface of the tracheotomy tube that resides in the trachea to allow for air to pass through into the upper airway.

FIGURE 71-1. Metal (Jackson) tracheotomy tube with inner cannula.

FIGURE 71-2. Plastic tracheotomy tube with and without inflated cuff, and with inner cannula in place.

A tracheotomy tube can be occluded with a finger, cork, or flapper valve. If there is an upper airway problem that prevents easy expiration out the mouth and nose, intermittent finger occlusion is used to allow for inspiration through the tube, but only for selected expiration via the upper airway during speech production. If there is no upper airway problem but a tracheotomy tube is required for airway maintenance, either short-term or long-term occlusion of the tube with a cork is appropriate. This eliminates the need for occlusion of the tracheotomy tube with a finger during speech. A special type of metal tracheotomy tube is a Tucker tube (Fig. 71-3). This is a sterling silver tube with an inner cannula that contains a one-way flapper valve. The flapper valve allows inspiration through the tube but then passively closes during expiration, diverting air around the tube via the upper airway to be used for voice production or simply exhaled. The Tucker tube is used when a tracheotomy tube is required for a longer time.

FIGURE 71-3. Tucker tracheotomy tube with inner cannula containing one-way flapper valve.

“Speaking” Tracheotomy Tube

The primary goal of a speaking tracheotomy tube is to allow cognitively intact ventilator-dependent patients to communicate verbally (25,28,29). The Portex “Talk” tracheotomy tube has been shown to be successful in allowing this population of patients to speak (29). It is a doublelumen, unfenestrated, single-cuffed tube designed with an external airflow line at the nine o'clock position. Gas travels through the airflow line, exits via a slit just superior to the cuff, and then continues up through the glottis and vocal tract to allow for speech production (Fig. 71-4). The user can occlude the airflow line for independent speech production or, if upper extremity paralysis or weakness prevents self-use, the listener can occlude the airflow line to allow for verbal communication.

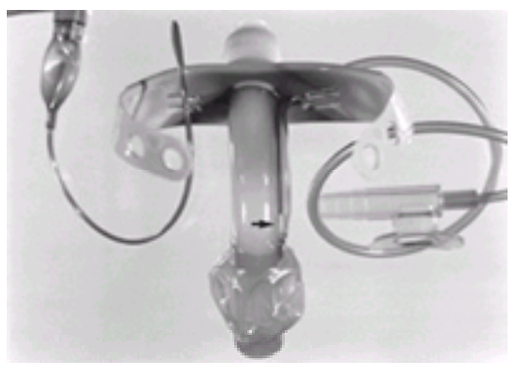

FIGURE 71-4. “Speaking” tracheotomy tube with external airflow line. Arrow shows slit where air exits.

One-Way Tracheotomy Speaking Valves

A one-way tracheotomy speaking valve attaches to the external hub of a tracheotomy tube, usually plastic, and permits inspiration through the tracheotomy tube, but on exhalation the tube is blocked and air must exit through the larynx and out the mouth or nose. Most one-way valves attach to plastic tracheotomy tubes (Fig. 71-5B, Fig. 71-5C, Fig. 71-5D), but a new one-way valve has been designed specifically to attach to a metal tracheotomy tube (Fig. 71-6). The one-way valves eliminate the need for finger occlusion. It circumvents the problem of a patient not tolerating permanent occlusion of the tracheotomy tube with a cork when he or she has an upper airway restriction such as tracheal stenosis, laryngeal web, laryngomalacia, or arytenoid edema (30).

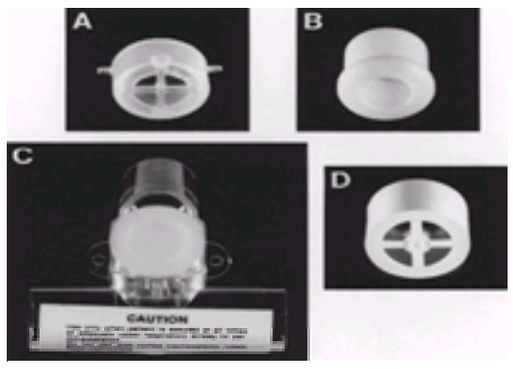

FIGURE 71-5. The four one-way tracheotomy speaking valves. **A:** Kistner, B: Montgomery, **C:** Olympic, **D:**Passy-Muir. (From Leder SB. Perceptual rankings of speech quality produced with one-way tracheostomy speaking valves. *J Speech Hear Res* 1994;37:1308, with permission.)

FIGURE 71-6. Passy-Muir one-way tracheotomy speaking valve for a metal tracheotomy tube.

Rehabilitation with a one-way tracheotomy speaking valve is straightforward. The tracheotomy tube cuff, if present, must always be deflated with valve use to allow for expiration around the tube and through the glottis and upper airway. Most patients require only a short acclimation period with the valve. During this trial period, the patient is told that breathing, especially expiration, may feel different because of the valve. If the patient experiences difficulty in breathing, continued trial periods of valve use, increasing in length, should be done to habituate the patient to the valve. A pulse oximeter can be used to monitor arterial oxygen percent saturation (30).

There are a number of different commercially available one-way speaking tracheotomy valves, for example, Kistner, Montgomery, Olympic, and Passy-Muir (Fig. 71-5). All have similar basic components, but they differ in their engineering and design. Each has a diaphragm that is either bias open (open at all times and closed only on expiration) or bias closed (closed at all times, inspiratory effort being needed for opening). All diaphragms close on expiration, and all valves attach to the hub of a tracheotomy tube. In addition, the Passy-Muir valve comes in two types, one for patients who are ventilator dependent and one for those who are not. The Passy-Muir valve has been identified with the best speech quality most often by both listeners and users, and it has also exhibited the fewest clinically relevant mechanical problems (30).

Total Laryngectomy: Alaryngeal Speech and Voice Restoration Rehabilitation

Unlike the consequences of surgery to the vocal tract, a total laryngectomy results in removal of the sound source itself: the true vocal folds. This obviously results in a significant problem for the resumption of verbal communication. The goal of voice restoration rehabilitation is to provide an alternative sound source to allow speech articulation, phoneme production, and meaningful verbal communication to occur. No one method for the alternative sound source is better than another. The goal is to match the method that is best for the patient at any particular time in the rehabilitation process.

The first 10–14 postoperative days can be divided into two distinct periods: immediate (1–4 days) and transition (5–14 days) (2). The immediate postoperative period is characterized by a reduced ability of the patient to interact with the environment; the recovery from the effects of general anesthesia; nonambulation; connection to monitoring equipment; and a greater level of discomfort from surgery than is evident in the transitional period. The transitional period usually includes ambulation; increased interaction with the environment as evidenced by writing, watching television, and resumption of oral feeding; and initiation of voice restoration rehabilitation with an electrolarynx.

Barring postoperative complications, the patient is usually discharged from the hospital after 10–14 days. Outpatient voice restoration rehabilitation continues the therapy begun during the transitional recovery period. Discussions with the speech-language pathologist regarding the use and timing of the various voice restoration techniques for verbal communication are carried out on a long-term basis so that an informed choice of optimal alaryngeal speech can be made.

Alaryngeal speech can be produced from four types of sources: (a) intrinsic (buccal, pharyngeal, and esophageal), (b) prosthetic (artificial or electrolarynx), (c) surgical (tracheoesophageal [TE] fistula or neoglottis), and (d) surgicalprosthetic (pharyngotomy with prosthesis or TE puncture with prosthesis) (31,32).

Intrinsic Voice Restoration

Intrinsic voice restoration does not rely on surgery or a prosthetic device. The sound source is produced by existing oral, pharyngeal, or esophageal structures. Buccal (“Donald Duck”) and pharyngeal (high-frequency and squeaky) speech are not desirable and should be discouraged.

Esophageal speech is a good goal but is not always obtainable. Esophageal speech is produced by injecting or inhaling air into the upper esophagus at the C-4 to C-6 level, thereby vibrating the walls of the pharyngoesophageal segment as the air is returned to the mouth (Fig. 71-7). Several methods can be used to produce successful esophageal speech using air injection and air inhalation techniques (cf. references 2 and 29 for detailed discussions). This new sound source has greater mass than the true vocal folds, and therefore the voice produced has a lower fundamental frequency. In addition, less air is available with esophageal speech than from the lungs, resulting in fewer words per air charge (33,34). It should be mentioned that not all total laryngectomees can achieve fluent and intelligible esophageal speech; some reports estimate that fewer than 10% of laryngectomees achieve acceptable fluency (31).

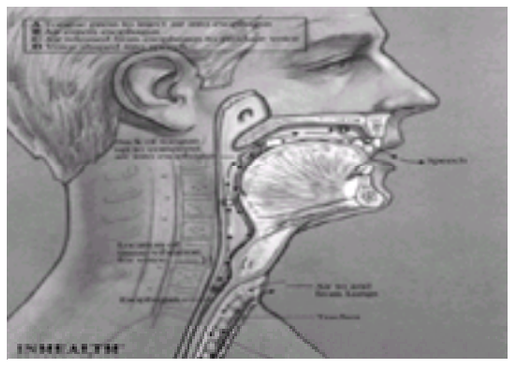

FIGURE 71-7. Esophageal speech (Inhealth Technologies, 1110 Mark Ave., Carpinteria, CA 93013-2918).

Prosthetic Voice Restoration with an Artificial Larynx and an Electrolarynx

An artificial larynx uses the laryngectomee's own lung air as the driving force for the new sound source. To do so, the artificial larynx connects the stoma with the oral cavity (Fig. 71-8). These devices are cumbersome to use, draw attention to the user, and are not generally used any more.

FIGURE 71-8. Artificial larynx.

An electrolarynx provides the new sound source by vibrating the air in the remaining vocal tract, either directly, as with an intraoral device, or transcervically, as with a neck placement device (Fig. 71-9). The devices have builtin sound generators that are battery driven, and they have on/ off, volume, and pitch controls that allow for some production of intonation and contrastive stress (35).

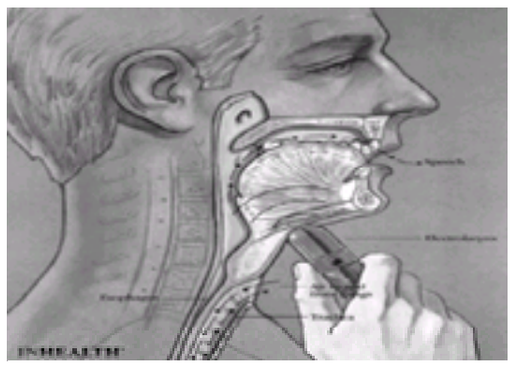

FIGURE 71-9. Electrolaryngeal speech (Inhealth Technologies, 1110 Mark Ave., Carpinteria, CA 93013-2918)

An electrolarynx should be provided to the new laryngectomee as soon as possible, usually 3–4 days postoperatively. Although optimal speech production and intelligibility are not obtained, the positive psychological benefits of voice restoration rehabilitation provided by early introduction of an electrolarynx far outweigh any frustration due to early use of the device for speech production. An electrolarynx can also be used during all voice restoration rehabilitation techniques.

There are three types of electrolarynxes: (a) those with an extraoral sound source and intraoral connector only, (b) those with an extraoral sound source with option of intraoral connector and transcervical (neck) placement, and (c) those with a totally intraoral sound source with extraoral control.

Figure 71-10 shows a typical device with an extraoral sound source and intraoral connector. Care must be taken so as not to block the end of the oral connector, and therefore the sound, with the tongue or with saliva. Optimal placement is usually 1.0–1.5 cm into the corner of the mouth between the buccal mucosa and tongue.

FIGURE 71-10. Electrolarynx with extraoral sound source and only intraoral connector [Luminaud, Inc. (Cooper-Rand Electrolarynx), 8688 Tyler Blvd., Mentor, OH 44060].

Figure 71-11 shows a typical device with an extraoral sound source but with two options for vibratory placement, intraoral and transcervical. The same technique as with the previous device (Fig. 71-10) is used with the optional intraoral tube. Approximately 1 month after laryngectomy, when the neck has healed and if neck induration is not a confounding factor, neck placement can be attempted.

FIGURE 71-11. Electrolarynx with extraoral sound source and both intraoral and transcervical vibratory placement options, with battery recharger (Siemens Hearing Instruments, Inc., 10 Constitution Ave., Piscataway, NJ 08855-1397).

When neck placement is used, the vibrator head should be pressed comfortably but firmly on the neck to allow the sound source to travel through the skin and vibrate the air in the vocal tract (Fig. 71-9). Experimentation with different neck placement positions and pressures is usually necessary before the best vocal quality and speech intelligibility are produced. Precise articulation, as well as correct use of the on/off button and correct placement of the intraoral connector or neck placement, is stressed. Variable pitch control can be achieved, if the device has two or more pitch controls, by neck tension or by placement of the device. It is important to remember that lung air is not needed for speech; therefore, stoma noise from exhaled air should be eliminated when an electrolarynx is used.

Figure 71-12 shows a device with a totally intraoral sound source with extraoral volume and pitch controls. The oral unit is custom-made to fit existing dentures or a new palatal retainer. The hand-held control unit houses the on/off, volume, and pitch controls and sends wireless radio commands to the oral unit, which houses the sound source and produces the desired pitch and loudness characteristics. The laryngectomee then uses the new vocal tract sound source for consonant and vowel articulation and phoneme production for intelligible verbal communication. The user holds the control unit out of sight in a pocket and does not have to use an intraoral or transcervical placement device.

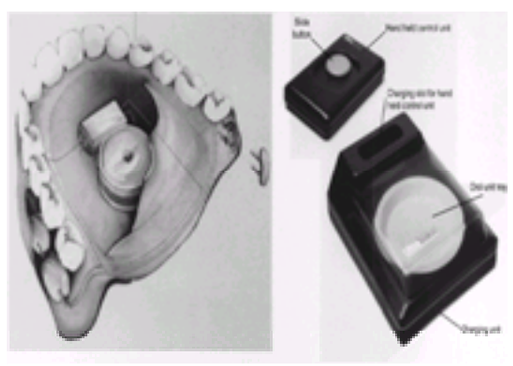

FIGURE 71-12. Electrolarynx with totally intraoral sound source and extraoral volume and pitch controls, with battery recharger [Health Concepts Inc. (Ultra-Voice), Inc., 279-B Great Valley Pkwy., Malvern, PA 19355].

Surgical Voice Restoration

Surgical voice restoration attempts to use lung air for speech by using various surgical techniques and the individual's own tissues, such as those of the esophageal mucosa, vein, skin tube, and tracheal tube (31). Unfortunately, unacceptable aspiration and tract stenosis leading to aphonia have occurred with most surgical procedure attempts. However, surgical voice restoration rehabilitation after total laryngectomy has not been abandoned completely (36), and innovative surgeons will surely continue to search for the optimal procedure.

Surgical-Prosthetic Voice Restoration Rehabilitation

Since the first reported successful total laryngectomy more than 100 years ago, many techniques, both surgical and mechanical, have been reported for speech restoration (37,38). Unfortunately, these early attempts were plagued by complications: aspiration, shunt stenosis, and fistula formation. Currently, the requisite essential for successful TE speech is a one-way prosthetic valve placed in the tracheostoma by a surgically created TE puncture, which permits expired air to be directed into the esophagus during tracheostoma occlusion but is closed at all other times to prevent saliva and food from entering the trachea (Fig. 71-13). The TE voice prosthesis is a hollow tube made of medical-grade silicone with a one-way valve at one end and retention collars on both ends (Fig. 71-14). Several different types are available, such as the Groningen button (39), the Provox (40), the Panje button (41), and the most widely used: the Blom-Singer TE prosthesis (42).

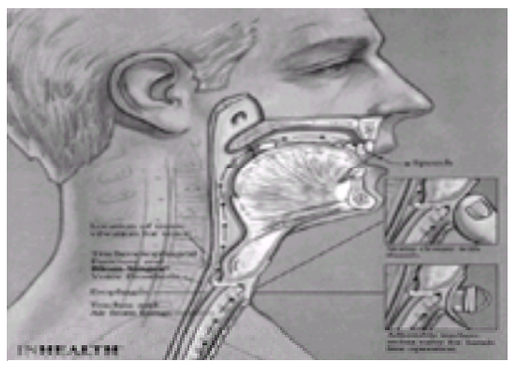

FIGURE 71-13. Tracheoesophageal speech (Inhealth Technologies, 1110 Mark Ave., Carpinteria, CA 93013-2918).

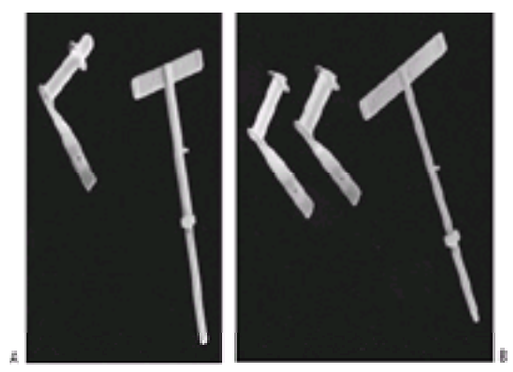

FIGURE 71-14. Blom-Singer tracheoesophageal voice prosthesis (Inhealth Technologies, 1110 Mark Ave., Carpinteria, CA 93013-2918). **A.** Duckbill voice prosthesis.

B. Low-pressure voice prosthesis.

The TE voice prosthesis resides in the puncture tract at all times to prevent stenosis of the tract and aspiration through the puncture tract. When the stoma is covered and exhalation occurs, air travels from the lungs, into the trachea, through the voice prosthesis, and into the esophagus. The esophagus vibrates, creating a new sound source, which sets the column of air in the vocal tract into vibration, allowing for speech articulation, resonance, and verbal communication to occur.

A common frustration experienced by TE prosthesis users is the need to change the prosthesis every 3–4 days. In fact, early (43,44 and 45) as well as later (46,47) studies reported as the greatest disadvantage of a TE prosthesis that it must be inserted and changed frequently by the user. Users found changing to be bothersome, difficult, or even impossible.

Recent product development advances, specifically the “gel cap” insertion method (48) and the extended-wear “indwelling” TE voice prosthesis (49), have eliminated this problem (Fig. 71-15). The gel cap provides a smooth, rounded configuration that transiently eliminates the retention collar. The gel cap then dissolves in 2–3 minutes in the esophagus, releasing the retention collar for internal anchoring. The indwelling TE prosthesis has larger retention collars on the tracheal and esophageal ends, is inserted and changed only by the speechlanguage pathologist or otolaryngologist, and can stay in place for as long as 6 months. Daily *in situ* cleaning with a flushing pipette is required of the user. Voice restoration rehabilitation is still required to achieve optimal speech intelligibility and pitch control by correct digital occlusion and pressure over the tracheostoma, and optimal use of a tracheostoma valve (48).

FIGURE 71-15. Blom-Singer tracheoesophageal voice prosthesis with gel cap insertion in place and extended-wear indwelling voice prosthesis (Inhealth Technologies, 1110 Mark Ave., Carpinteria, CA 93013-2918).

TE speech has been a viable and proven alternative to esophageal and electrolaryngeal speech for patients with total laryngectomy since the introduction of the Blom-Singer TE puncture technique and prosthesis in 1980 (42). Subsequent studies evaluating the TE puncture procedure and TE prosthesis speech rehabilitation by its developers (38,50,51), and, more importantly, by independent investigators (43,45,52,53,54 and 55), have shown both the procedure and the prosthesis to be reliable for TE speech production after total laryngectomy.

As stated in their original paper, “Although this [TE puncture] method appears uncomplicated, it is not always 'easy' and a number of factors must be considered” (42:532). Some factors are surgically or medically related, e.g., tracheostoma size and position, cricopharyngeus spasm, and irradiated tissue. Other factors are patient related, e.g., motivation, capability to care for the stoma and prosthesis, visual disturbances, and arthritis. Still other factors are speech-rehabilitation related, e.g., ability to follow directions, position and pressure for optimal digital stoma occlusion, TE valve use, and necessity of adequate follow-up (38,53,54). In all cases, the speech-language pathologist and otolaryngologist are a team that jointly selects, rehabilitates, and follows-up the patient with a total laryngectomy and TE prosthesis (42,52,56,57).

The TE puncture procedure can be done primarily at the time of total laryngectomy (54,58) or secondarily either after or in conjunction with esophageal and electrolarynx speech rehabilitation (42,55). A cricopharyngeal myotomy is done at the time of total laryngectomy during a primary puncture procedure. When a secondary puncture is recommended, transnasal insufflation testing is performed to assess pharyngeal muscle response to esophageal distention (59). The insufflation test assesses cricopharyngeous spasm, and a cricopharyngeal myotomy (60) or pharyngeal plexus neurectomy (61) may be necessary to allow for the fluent production of TE prosthesis speech.

The new sound source does not necessarily have to be the esophagus. In patients with extensive disease, a pharyngolaryngoesophagectomy with gastric pull-up may be necessary. Reconstruction may also include microvascular free tissue grafts, myocutaneous flaps, cervical flaps, and visceral transposition. The standard TE puncture procedure has been shown to be successful in voice restoration rehabilitation with this population, although the resulting voice is characterized by lower pitch, reduced intensity, slower rate, and an overall “wet” or “gurgly” quality in comparison with TE prosthesis speakers (62).

Tracheostoma Valve

The tracheostoma valve was developed to eliminate the need for manual occlusion of the stoma to divert air into the voice prosthesis for speech production (63). The valve system has several parts. The circular valve housing is glued to the skin around the stoma every day. The adjustable valve fits into the housing, and its diaphragm remains open during normal respiration but closes with increased expiratory airflow, thereby diverting air into the voice prosthesis and esophagus for hands-free speech production (Fig. 71-12 and Fig. 71-16). The diaphragm opens automatically when the user stops talking to allow for resumption of normal inspiration.

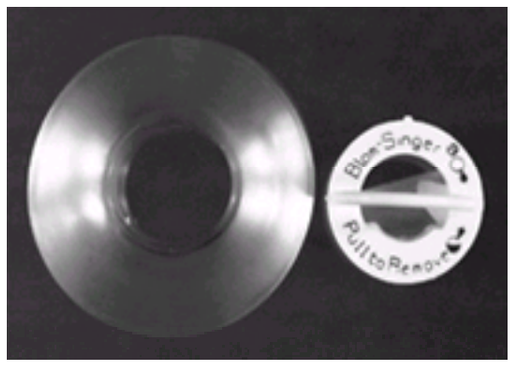

FIGURE 71-16. Blom-Singer tracheostoma valve (Inhealth Technologies, 1110 Mark Ave., Carpinteria, CA 93013-2918).

HEARING LOSS

Hearing loss goes hand-in-hand with speech production in the communication cycle (64). If hearing is impaired, the potential is great for the communication process to fail. For the individual with cancer, participation in the care plan, family discussions, conferences with caregivers, and informed consent for therapeutic decisions all rely on functional hearing. In addition, maintenance of orientation to the activities of daily living via the telephone, television, and radio are made much easier with the ability to hear at least as well as before treatment.

There are two types of hearing loss: conductive and sensorineural. Any impairment of the outer or middle ear with a normal inner ear results in a conductive hearing

loss. The difficulty is not with the perception of sound but with the conduction of sound to the analyzing system. The severity of the conductive hearing impairment ranges from slight to moderate: 15–60 dB hearing level (65). When the loss of hearing is due to a pathological condition of the inner ear or along the nerve pathway from the inner ear to the brainstem, the loss is called sensorineural. The severity of the sensorineural hearing impairment ranges from slight to profound, that is, 15–91 dB hearing level (65). There also can be a mixed hearing loss, involving components of conductive and sensorineural loss, affecting both sound conduction and sound perception.

Chemotherapy

Ototoxic chemotherapeutic drugs such as cisplatin have the potential to cause damage to the inner ear: the cochlea, vestibule, semicircular canals, and otoliths (66,67). The benefits of ototoxic therapy must be balanced with its potential for permanent damage to the inner ear and the resultant sensorineural hearing loss or balance disorders. Hearing and balance disturbances can have significant negative vocational, educational, and social ramifications. In an effort to minimize or even prevent ototoxic damage, audiologic testing before treatment and at regular intervals during and after treatment should be done. A comprehensive manual delineating guidelines for the audiologic management of individuals receiving ototoxic drug therapy is available (68).

External Beam Radiation Therapy

Osteoradionecrosis of the temporal bone after EBRT for malignant disease of the head and neck has been well described (69,70,71 and 72). Radiation can produce both early and late changes, ranging in time from 9 months to 20 years (73).

Hearing loss in 36% of irradiated ears has been reported to be caused by EBRT (74). Both types of hearing loss can occur. Osteoradionecrosis of the ossicular chain (75) and impaired eustachian tube functioning, which can lead to otitis media, can cause conductive hearing loss. Cochlea damage secondary to EBRT can lead to sensorineural hearing loss (74). Both conductive and sensorineural hearing loss can occur, depending on the extent of the radiated field.

Aural Rehabilitation

Aural rehabilitation for patients with hearing loss secondary to cancer or its treatment may be different from aural rehabilitation for other adults with hearing loss (76). Cancer patients may be depressed or weak from the disease and its treatment. The hearing loss, if conductive, may be transient and will improve spontaneously, for instance, when EBRT has been completed. The hearing loss, if sensorineural, may or may not be amenable to improvement with hearing aids. If cost is an issue, low-cost alternatives—assistive listening devices such as pocket amplifiers and telephone receiver amplifiers—may provide the extra volume needed for hearing and successful participation in the communication dyad instead of hearing aids.

Appropriate communication strategies with the person who is newly hearing impaired should be stressed. Strategies include proper positioning of the speaker and listener for unobstructed vision, placement of the hearing-impaired listener in close proximity to the speaker, elimination of interfering background noise, and good lighting to take advantage of visual cues. In other words, conversation should not take place in a poorly illuminated and noisy environment, as is the case in most hospital rooms, and with the caregiver or listener performing tasks in the room that make optimal visual and auditory input impossible (76).

CONCLUSION

The restoration of the best possible verbal communication is the goal of rehabilitation for people with impaired speech skills. Verbal communication, a uniquely human behavior, is critical to the patient's medical care, psychological functioning, and social interactions. Although cancer and its treatment may significantly alter the patient's ability to communicate verbally, many successful therapeutic interventions are available for the restoration of intelligible voice and speech production.

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72

MUSIC THERAPY AND ART THERAPY*

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PAOLA M. LUZZATTO

Music and art are forms of human expression that have been used throughout time to heal, to establish communication, to gather communities, and to portray inner thoughts, feelings, experiences, and intentions. These creative mediums are universally accepted and called on during times of celebration, reflection, mourning, and transition. The multidimensional characteristics of music and art offer rich resources for aiding human dilemmas and conditions of adversity.

Music therapy and art therapy have become familiar approaches in working with patients contending with life-threatening and terminal illnesses. These therapies are identified as nonpharmacological treatment modalities offering a range of calming and expressive benefits to patients and families. Interventions are offered by trained music and art therapists to facilitate meaningful changes in physiological, psychological, social, and spiritual processes. In this chapter, the use of music therapy and art therapy in this context is reviewed. In addition, a theoretical model is presented that describes the therapeutic process that may occur with supportive interventions. Case examples are reviewed as ways to demonstrate the use of these therapies in supportive oncology and palliative care.

MUSIC THERAPY

Music therapy became a formalized profession in both the United States and in Europe in the mid-twentieth century. Originally, music therapy was used as a means for aiding ailing veterans returning from war. As degree programs in universities began to formalize the education and training of music therapists, the profession expanded to work in collaboration with health care providers in psychiatric and medical institutions. Today, music therapists, having completed degree and national certification requirements, are employed worldwide in a range of health settings.

Music therapy has been found to provide many benefits to patients, families, and significant others. The literature describes the effectiveness of music to break the cyclical nature of pain (1,2), to alter mood (3,4), to promote relaxation (5,6,7 and 8), and to improve communication (9,10,11,12 and 13). Music therapists have refined methods for treating anxiety in children (14) and adults (15). Music therapists and health care professionals have begun to research the impact that music has on the various components of the human experience in life-threatening and terminal illnesses, that is, physiological (improved cardiac, respiratory and adrenal functioning as well as decreased symptoms of nausea, insomnia, or fatigue), psychoemotional (alteration in mood and enhanced coping styles), and social (enhanced communication) (16,17,18,19 and 20).

During the past decade in particular, the use of music therapy in palliative care settings has increased substantially. Music therapists have begun to write extensively about clinical experiences and research in working with the seriously ill and dying and with their significant others. Theoretical models and methods of treatment have been developed and are being used by music therapists in the areas of pain management, music and neurological sciences, music psychotherapy, and integrative medicine.

Pain Management

Music therapy is one of the nonpharmacological treatments for pain and associated symptoms. Music therapists provide expressive methods to facilitate relief from suffering (1,21,22). In the management of pediatric pain, Loewy (23) has emphasized that the assessment of emotional and physical parameters determines the use of appropriate techniques. Other music therapists routinely use specific techniques such as entrainment—the use of sound stimuli to match and then alter responses (21,24). Other therapists use physioacoustic therapy, which is the use of pure sinusoidal sound waves (25) and nonrhythmic, slow tempos and low frequencies (26). More and more, music therapy is being used in the treatment of pain in cancer and advanced illnesses.

Music and Neurological Disease

Music can affect neurological mechanisms. Because hearing is the first sense to be developed and the last sense to deteriorate (27), music is a particularly effective stimulus to reach and make contact with patients who are otherwise not responding to words or touch. This attribute of music is relevant in work with advanced illness. Music can help restore relatedness, thereby reducing isolation or providing for moments of meaningful communication between patients and family members.

Research has clarified the impact of music on patients with neurological disease, such as brain tumors, central nervous system lymphoma, and metastatic illness. At the Instiute for Music and Neurologic Function in New York, Tomaino (working with Dr. Oliver Sacks) uses music as a “retrieval mechanism” to help patients with memory impairment recall significant events (28). For patients who have expressive aphasia, singing can facilitate renewed expression and articulation within the context of music (11). In studies by Rider (29), improvisational music therapy with entrainment is found to influence psychoneuroimmunological responses. This is explained in a theory of homeodynamism, that is, the neurological shifting and synchronization of electroencephalogram patterns.

Music can ameliorate pain and symptoms of fear, anxiety, depression, frustration, and loneliness. Thorough assessments guide the music therapist to offer interventions that best suit overall needs. Although there may be times when no music is used, such as with acutely distressed patients who may not be able to manage any surfacing of emotions, music has unique potential to operate multidimensionally, interacting simultaneously with physiological, psychological, emotional, social, and spiritual processes.

Music Psychotherapy

Music therapists are applying psychotherapeutic skills in the care and treatment of persons contending with advanced illness. Loewy (30), for example, uses music psychotherapy with children to facilitate expression and the processing of issues. Analytic music therapy has been found to benefit some adults through the uncovering of issues surrounding symptoms, some of which are psychosomatically based (31). Music therapists may base clinical work in various models of psychotherapy and attend to the multifaceted needs and issues presented by patients and significant others.

Integrative Medicine

Integrative medicine programs may offer music therapy as one of the complementary therapies in mainstream medical care (16). Music therapists work in conjunction with multidisciplinary team members as partners in the care of patients and families. The aims are to facilitate well-being and improve quality of life, providing music-therapeutic relationships within which persons can express, explore, improve communication, and process issues concerning living and dying (22,23,32,33,34 and 35). The term *medical music therapy* is used to describe the role that music therapists have in mainstream medicine today (36).

Clinicians have documented the use of melodic and improvisational music in populations with breast cancer (37) and human immunodeficiency virus/acquired immunodeficiency syndrome (38,39,40 and 41). Other techniques, which have been described by practitioners who are not boardcertified music therapists, include the use of specific melodic music during the active process of dying (42), Tibetan crystal bowls and vibrational tones, and tools such as tuning forks. Music therapists sometimes incorporate variations of these techniques into their clinical work as a means to improve physiological functioning, enhance relaxation, and diminish awareness of pain.

Music therapists elaborate on the essence of the musictherapeutic relationship that resides in the human contact and the supportive, caring presence of the therapist (34,43,44). Music therapists realize the significance of their roles in establishing a compassionate, attentive, and creative milieu, within which patients and families can explore and regain a sense of dignity and existential meaning.

ART THERAPY

Art therapy started in the United States and in Europe in the 1940s and became recognized as a discipline and as a profession, with postgraduate university training programs and national associations, in the 1960s and 1970s (45). Although most art therapists work with psychiatric populations, art therapy has slowly developed into other fields, such as education, social services, and medical care. Approximately 20% of the art therapists in the United States are currently working with medically ill populations.

The term *medical art therapy* is now being applied to the use of art therapy with individuals who are physically ill, experiencing trauma, and undergoing aggressive and longterm medical treatments (46). During the 1980s, cancer centers and hospices started to welcome art therapists into their multidisciplinary teams, and the trend has been increasing. In England, a “special interest” group of art therapists working in palliative care was formed in 1993. This group, known as “The Creative Response,” aims to work “with the whole person,” according to the definition of palliative care given by the UK National Council for Hospice and Specialist Palliative Care Service: “controlling pain, easing suffering and enhancing life . . . integrating psychological and spiritual aspects of care . . . and offering support to families during the patient's illness and their bereavement” (47).

The writing of art therapists who work with patients in pain is relevant to the field of palliative care. From work with burn patients, Russell (48) developed a useful model of art therapy to help the physically traumatized patient move through five different stages: (a) expressing anxiety, (b) providing relaxation, (c) offering search for meaning, (d) providing a reparative experience of creativity, and (e) dealing with loss and mourning. Landgarten (49) also describes work with a chronic pain patient as a series of steps, including overcoming the need of denial, ventilation of fears, release of rage, and mourning. Long (50) lists four ways of using art therapy in a pain management service: (a) focused work to evaluate pain levels, using drawings of pain in the body and collage work to connect the pain with psychosocial stressors; (b) free drawing to allow and deepen the expression of the pain experience and its transformations; (c) family art therapy, when there is a dysfunctional dynamics in the family system; and (d) drawings about pain before and after physiotherapy to reinforce positive changes.

Rosner-David and Illusorio (51) have provided art therapy to patients with tuberculosis and have focused their work on the special needs of patients in isolation. Others have used art therapy to help patients suffering from acquired immunodeficiency syndrome; the approaches have ranged from individual single sessions to ongoing groups (52,53,54 and 55). Some of the most significant contributions from art therapists working with medically ill patients, specifically in palliative care, are included in three volumes published in the late 1990s (56,57 and 58).

The use of art therapy with children has been developing over the years. Art therapy with medically ill children may start from the body and the visualization of pain (59) and move to the broad area of the child's thoughts and emotions (60,61,62,63 and 64). It also may include the challenging and often forgotten field of children's spiritual needs (65). Councill (66) shows that art therapy may offer important contributions to any pediatric unit, at all stages of the child's illness: diagnosis, maintenance, and advanced-stage. Favara-Scacco (67) describes the use of art therapy techniques to support children with leukemia during painful procedures: the “clinical dialogue” to explain the medical procedures; “visual imagination” to activate an alternative thought; “medical play” to increase in the children a feeling of control; and both “free” and “structured” drawings to help them externalize and contain feelings of confusion, loneliness, and fear.

Stimulating reports have appeared that describe the use of art therapy with laryngectomy patients (68) and with mastectomy patients (69). Camic (70) explored the combination of different expressive modalities for the relief of chronic pain and Hiltebrand (71) described the use of different techniques of visualization and image manipulation. Minar (72) reflected on symbolic imagery in an art therapy group with cancer patients and described the recurrent images of the “hurter” and the “healer.” The use of mental and visual imagery to help cancer patients deal with their illness has been explored by Archterberg (73). Riley (74) illustrated the role of art therapy to facilitate communication and decrease the stress within the family and Belfiore (75) described the use of supportive art therapy to decrease stress in health care providers.

A range of innovative art therapy interventions is being developed to treat cancer patients in hospitals, hospices, and private homes. Connell (76,77 and 78) pioneered the use of art therapy with cancer patients at the Royal Marsden Hospital and experimented with special open groups, poetry writing and readings, and group notebooks containing new images and reflections made by the patients. These notebooks were designed to be looked at and read by the other patients, as a form of ongoing communication.

Thomas (79) described how it is possible to “create a space for stillness” for patients in the hospice. A 10-week art therapy program called “The Creative Journey” has been devised by Luzzatto in the Department of Psychiatry at Memorial Sloan-Kettering Cancer Center (80) to address the needs of patients undergoing bone marrow transplantation and having to be in isolation for long periods of 6–8 weeks (81). McGraw (82) described how the studio-based model of art therapy may help patients with chronic illness and pain focus on their healthy side, and Bell (83) has developed an “adaptive theme-oriented approach” for terminally ill patients in their own homes, in which issues of ill health, pain, suffering, aging, and dying emerge and are visualized and shared in the friendly setting of the family's kitchen.

It has been pointed out that art therapists working with the terminally ill have to be aware of their own responses to the existential themes of illness and death (84). In her review of the literature in the field of art therapy in palliative care, Wood (85) concludes that art therapy seems to be able to touch on “all aspects of the person's being.” This may be the specific contribution of art therapy—that it can provide “an experience which can address physical pain, can facilitate a search for meaning, can provide an outlet for strong feelings and can enhance the person's quality of life” (85).

STAGES OF THE THERAPEUTIC PROCESS IN MUSIC AND ART THERAPY

Although research in the effectiveness of the arts-based therapies is still scarce, numerous reports suggest that cancer patients may benefit in a special way from the use of creative modalities such as music therapy and art therapy. These expressive mediums can soothe pain as well as stimulate imagery and association, promote release of buried emotions, and provide creative spaces for the discovery or rediscovery of the inner self.

The connections between music and art are natural and obvious, as music and art are together part of the creative arts world. Music and art therapies are different professions, however, and make use of inherently unique therapeutic modalities. These modalities are based on two different senses—*hearing* and *sight*— and emphasize two different communicative dimensions—*time* in music therapy and *space* in art therapy.

The goal in music and art therapies is to facilitate expression and elaboration of the patient's internal world. Music and art therapists offer special tools to fulfill the same aims. The following is a summary of therapeutic factors that are characteristic of both music and art therapies and are particularly relevant in the cancer population.

1. *The protected expression of the negative.* Any “negative” experience, from physical pain to disturbing memories and emotions, may be expressed in a protected way, through the indirect and symbolic route of colors, shapes, and sounds. The patient may create a rhythm or melody or make an image, without explaining to anybody what it refers to, and possibly without knowing what it may refer to. Even when the physical sensation is about pain and the mental state is about suffering, the personal translation into sounds and images may give the patient important feelings of control and autonomy.
2. *The strengthening of the positive experience.* The creative process involved in the expression through musical instruments and art materials seems to have the capacity of transforming moods. This may happen in two directions: from active to receptive and from receptive to active. A patient who feels anxious may use sound-making, songs, or image-making to feel more relaxed. Likewise, a patient who feels fatigued and depressed may use different forms of these techniques and may start to feel pleasure and energy.

3. *A step toward verbal communication.* At times, the created piece of music or art may be an unconscious communication towards a relative or member of the staff. Other times, the communication may be conscious and intentional, i.e., the patient may “want” a relative to listen to his/her piece of music, or may “want” to show a certain image. After the first step of nonverbal communication, very often the patient desires to add words to the sounds, such as in songwriting, or to the image. Quite often the door is open at this point to say more and to feel more connected to others.
4. *Musical and visual elaborations.* Music and art therapists try to establish contact and break barriers, fill emptiness, and facilitate a psychoemotional “flow” in their patients and their significant others. The patient may feel no energy, or no hope or interest in what is happening inside (or outside) of self. It may be that the patient is feeling frustration, fear, or sadness—these feelings are forms of barriers. The music therapist knows that a sound stimulates another sound; the art therapist knows that an image leads to another image. The “flow” of the music and visual creation is very important, as it becomes a stimulus for the flow of the patient's own energy.
5. *Self-narrative and self-awareness.* Although music and art therapists have their own techniques to stimulate the patient's self-awareness and narrative, they both essentially use two main tools: nonrational “free association” and the more rational effort of “making sense” of what has emerged through the free association. Series of sounds or lyrics in songs may become personal songs, and series of images may become personal stories. These forms of self-exploration and self-revelation are usually connected to an experience of discovery about the self.
6. *Dealing with existential and spiritual needs.* Patients in palliative care settings are faced with questions about pain and quality of life, loneliness and life meaning, life and death. They do not necessarily have the answers to these questions. Care for “the whole person,” however, implies attention to this aspect of their lives. Music and art therapists realize that music and art offer the creative, lyrical, or symbolic means to address existential and spiritual needs during the process of dying.

INTERVENTIONS

Music Therapy

In working with patients who have life-threatening illnesses and their families, music therapists employ methods to attend to multifaceted needs. Regular and thorough assessments are critical to facilitate comfort and provide for meaningful expression and elaboration. Through questioning, observation, and interdisciplinary collaboration, therapists gain a perspective on the patients' perception of pain as well as the functions that affective, cognitive, and sensory processes are attributing to the experience. Music therapists become acquainted with prior musical skills, i.e., “music listener” (one's primary experience is as a listener), “music performer” (one has had numerous experiences as a performer), or “music eventer” (one associates music primarily around events in life) (5), to reestablish a sense of identity and to support the integration of music into the therapeutic process. Music therapists strive to create a musical space into which persons can enter, a space that invites reflection, identification, and exploration of thoughts, attitudes, memories, and emotions. Music is used that reflects the mood and overall needs, and is chosen and created by the music therapist, patient, and significant others. It is within this therapeutic milieu that symptoms of suffering may be alleviated.

Music therapy sessions can take place in various locations. Work is generally done at the patient's bedside, although work can also be done in clinic rooms, music therapy rooms in offices and outpatient centers, or at home during home care visits. Music therapists generally use a selection of instruments in their work, such as guitar, keyboard, harp, autoharp, stringed or woodwind instruments, crystal bowls, and percussion instruments. Patients and family members are offered opportunities to spontaneously create the music or to play or listen to favorite selections, live or recorded, of instrumental or lyrical music. The therapeutic aims are to facilitate self-discovery and enhance personal well-being, whether it is through the use of precomposed songs, instrumental and lyrical improvisation, toning and chanting, the use of imagery in music, or listening techniques.

Five case examples illustrate the types of interventions used by the music therapist. These patients were treated through the Music Therapy Program of the Integrative Medicine Service at Memorial Sloan-Kettering Cancer Center.

Use of Precomposed Songs

Songs are unique forms of musical presentations in that they combine words with rhythms, melodies, and harmonic tones. Precomposed songs are dynamic tools for use in music therapy because they convey thoughts, speak of feelings, and tell stories about the tribulations of humankind; or they present themes—such as love, faith, hope, or loss. Patients may select songs that reflect messages that are foremost in their thoughts, such as those reflecting deep yearnings, insecurities, or sorrows, or they may choose songs reflecting personal beliefs concerning life and meaning (86,87). Songs can be used to facilitate expression of “negative” and “positive” experiences in safety and may be used to promote communication. Often the patient is not conscious of the lyrical connections to immediate circumstances. However, choosing, singing, and listening to songs provides less threatening vehicles of expression among patient, family, and therapist, often deepening awareness of unresolved issues. Songs are also beneficial with emotionally fragile patients who may need the structure of words to guide frightening images and thoughts.

Case Example

Carl, age 28, was diagnosed with lymphoma after a 12-year remission from childhood Hodgkin's disease. He was recently married and had been leading a normal life before this onset of disease. He was referred to music therapy by the Supportive Care Program due to his intense neck and shoulder pain and his high levels of anxiety and tension. His verbal communications were limited to “yes” and “no” statements.

The music therapist approached Carl and offered to sing a song of his choice. He refused to select, but stated that he would like to hear music. The music therapist chose songs that reflected home and country, such as “Take Me Home Country Roads.” Carl rested on the bed and gazed at the ceiling. During the next session, Carl asked the music therapist if she knew the song “Mr. Bojangles.” During the song, he faced the therapist and stared intently at the guitar. He asked her to sing it again, only “this time, sing it louder.” She did, and when she arrived at the verse that stated: “his dog up and died, and after 20 years he still grieves,” Carl shouted, “louder, louder!” He asked her to sing the song several times that day as well as in the ensuing sessions, during which he repeated his requests for loud singing during the verse that spoke of loss and grieving. After several weeks of music therapy sessions during which Carl repeatedly requested to listen to “Mr. Bojangles,” Carl began to speak to staff and family members about his sorrow and grief, his desires to return home and to live the life that he knew.

In this example, precomposed song material provided a safe vehicle through which the patient could begin to express and process feelings of loss and sorrow in ways that could not be verbalized at that time. The opportunities for expression in this way helped mobilize his feelings as he moved from “protected expression” to “self-awareness.” He was then able to reestablish meaningful communication with others.

Improvisation

Instrumental and vocal improvisation offers opportunities for spontaneous expression in music, release, communication, and discovery. Because creativity can take any direction during improvisation, sounds, melodies, and rhythms can be played to portray the self through music in any way the person chooses. Thus, the music becomes a landscape of sounds that may depict deep inner feelings or thoughts. Improvisation is often done with the therapist offering support on the same or another instrument, providing the quality of “being heard” that is invaluable in therapeutic relationships. The use of the voice in improvisation adds the unique attribute of intimacy, because the voice is the most intimate means of self-expression. The voice can accompany instruments or can be improvised solo, with or without the addition of chosen lyrics. Vocal improvisation can include spontaneous songwriting with lyrics that articulate personal messages. Improvisational techniques provide for unconscious or intentional disclosure of emotions and can lead to deepened awareness, self-identity, and relatedness with others. Common improvisation techniques include active playing of instruments to express self, listening to improvisations that may reflect moods or images, and songwriting.

Case Example

Alex, age 57, was an academic achiever, with numerous professional roles in the education and health care professions. He was referred to music therapy due his agitation, restlessness, and pain. At the time of referral, he was in the advanced stages of lymphoma and was receiving chemotherapy to diminish some of his distressing symptoms.

The music therapist visited Alex and explained the potential for music to help express (as well as to diminish) pain. After listening to quiet reflective music of his choice, Alex appeared calm and relaxed until another staff member entered and offered to help move his swollen legs. He then became agitated, only reluctantly agreeing to let her help him.

The music therapist then offered the keyboard to Alex. He situated it on his lap in bed and began to slowly play 8- to 10-note, free-flowing melodies. He played for nearly 20 minutes nonstop, and directed the music therapist to stand near him with the guitar to strum with him. She followed his music by combining notes with chords. He played with intensity and determination and then requested to play for his wife as she entered the room. He became energized and immersed in the sounds. His wife stood by his side and listened to the lengthy improvisation. When he finished, he said, “That was my concerto. When can I do this again?”

The music therapist offered to return the next day and following days. Alex continued to use improvisation and began to have a renewed sense of identity and feelings

of control. His agitation diminished as he found new ways to create and direct the outcome of certain events. He also began to compose songs with the music therapist articulating his feelings of love for his family, his feelings of satisfaction concerning his accomplishments in life, and his feelings of sorrow regarding his approaching death. One song in particular was his favorite, a song that he and the music therapist wrote about his success in rescuing a mother and baby dolphin, also seeming to speak poignantly of his deep love for his family:

> “eye to eye, heart to heart, in spirit we're never apart;
> I trust you, you trust me, Oh dolphins of the sea.”

In this example, improvisation offered the patient meaningful exploration and sensitive communication with his family during a time of pain and loss. This technique allowed the patient free space to express suppressed feelings and experience a renewed sense of self-worth in taking an active role to provide for his wife and family. As seen in this example, the spontaneity that is characteristic in improvisation enhances interrelatedness between patient and others and opens passageways of communication.

Chanting and Toning

Chanting and toning have been used for centuries in indigenous cultures as ways to commune in fellowship, achieve spiritual enlightenment, and gain physical comfort or strength. Toning has been used as a method in spiritual practices to improve spiritual and physical well-being. Likewise, chants are common to every culture as a means to focus intention and unite in purpose.

These techniques are useful in therapeutic arenas as methods to promote attentiveness and relaxation. Toning is the use of vocalized vowel sounds at various pitches (88). Toning is used in music therapy to stimulate energy flow and enhance sensory awareness. Music therapists work closely with patients in pain to engage cognitive processes—that is, to actively vocalize and “breathe” sound “to,” “in,” “around,” and “away from” the pain. Such vocalizations, when possible, can energize and bring the release of tension and the eventual refocusing of attention. The technique of toning also offers the patient a tool that he or she can use during pain episodes, such as vocalizing with exhalations to express the pain, release tension, and refocus attention.

Chanting is similar in that vocalizations are repetitive (89). Chanting, however, includes the dynamic of tempo and the use of words that are purposefully selected by the patient and family. Music therapists establish a rhythmic pattern that is suitable to the moment, often matching the patient's rate of respiration and then changing to a tempo that could potentially result in relaxation. This use of rhythm follows the familiar music therapy method of entrainment, wherein sound stimuli “lock in” and can influence the flow of physiological responses such as heart rate and breath rate (90). The repetitive nature of chanting is soothing and lulling. The words selected often reflect desire, hope, faith, or personal strengths. Chanting, then, can result in increased awareness, improved levels of comfort, and a restored sense of self-efficacy.

Toning and chanting are beneficial to those seeking tools to help themselves regain a sense of control, as well as those with difficult-to-manage pain who are hoping to find ways to call on their inner resources. However, toning may not be suitable for emotionally fragile patients, who may need the direction and guidance of structured music, such as songs or formal compositions, to help assuage hyper reactions or to placate frightening images and feelings of apprehension. Toning and chanting can, however, help mitigate symptoms for many patients and families.

Case Example

Bonnie, age 56, was admitted to the hospital for the first time shortly after her diagnosis of stage IV ovarian cancer at another medical center. She had just received the news of her advanced disease and was told that she could receive chemotherapy as an attempt to deter further progression of disease. She agreed and planned to stay for treatment. The nursing staff referred her to music therapy due to her pain, fear, and overwhelming anxiety.

As the music therapist went into the room, Bonnie spoke quickly and said “please come in and stay by me . . . I am so afraid.” She was alone, and, leaning back on her bed, appeared to be in discomfort due to abdominal distention. The music therapist sat near Bonnie and listened to her relate her story. Bonnie wept as she talked and shared how out of control she was feeling. After she finished talking, the music therapist offered music therapy and Bonnie was eager to try.

Because the initial goals in music therapy are to attend to immediate needs, the music therapist offered toning and chanting to help Bonnie regain focus and sense of control, while also providing her space within chanting to begin to further articulate her feelings and thoughts. She leaned back on her pillow while the music therapist sat near her and made soft tones, progressing from low to high. At the start, Bonnie made some sounds too and then fell asleep.

Bonnie requested toning sessions daily. She also began to chant images of favorite places and words describing her attributes. Often, her close friends joined in the sessions, surrounding her bedside. Bonnie exclaimed that the toning and chanting refreshed her in ways that “words can't describe” and that she had a regained sense of self-identity. She became less anxious and more relaxed. After discharge, she went home for 2 weeks before she died, during which her friends toned and chanted with and for her at her side.

In this example, these techniques became important tools for the patient to use to renew her fleeting sense of self. Through opportunities to “hear” her own voice and to “feel” the sound vibrations within her, Bonnie was able to “feel” in touch with her physical self once again, as well as be in touch with the “chanting” words that had special meaning to her.

Imagery in Music

The use of imagery within the context of music is a technique that can be used with active or receptive participation. The active use of imagery in music is beneficial for patients who are encumbered by long periods of anxiety or isolation. It can open pathways of communication regarding buried emotions or memories of significant events. This technique can offer opportunities for “protected expression,” to explore images and the related feelings that arise in the music within sessions. Thus, the active support of the music therapist is vital. The receptive use of imagery in music may be offered to patients who have episodic pain, nausea, insomnia, or other disease-related symptoms. Receptive use of imagery is also used with patients who may be too weak to articulate thoughts. Patients may benefit from focusing on images to guide thoughts, help calm anxiety, or focus on the “pleasing” sensations of the music. The therapist inquires about the images that are helpful to the patient and then spontaneously sings the images, encouraging the patient to relax breath flow and tension and to “drift” with the music.

Case Example

Ann, age 63, was referred to music therapy due to pain associated with advanced breast cancer. She was a nurse specializing in gerontology and had lived a very active life until this admission. She smiled broadly when the music therapist entered the room. She was alone sitting quietly in bed. She talked briefly about her “difficult-to-cope-with” pain, but then changed the subject, relaying her love for the sea and how she missed seeing it that summer. She closed her eyes and leaned back on her pillow. The music therapist began to play the guitar softly, encouraging Ann to look out over the water during the music. She then asked Ann to convey what she saw in her internal gaze. The therapist then sang a progression of images, moving over the sea and describing the colors, sounds, smells, and views clearly.

> “blue calm waters all 'round me”
> “wide blue sky now over me”
> “warm sea sand now covering my feet”

While listening, Ann appeared deeply relaxed. As the music continued, she suddenly raised her arms gently and moved them up and down. The therapist followed her movements with the music. She whispered, “I am flying and my shoulder isn't hurting.” The music continued until Ann rested once again and fell asleep.

During later sessions, Ann requested to receptively engage in imagery in music. She selected the places where she wished to travel with the therapist in the music. She routinely became relaxed and often smiled peacefully. She repeatedly claimed that the music helped her pain “drift away.”

The use of imagery in music helped this patient, as it does others, transport attention into places of interest. This process, while aiding in the reduction of awareness of pain, can instill a sense of peace. Images relating to memories can sometimes evoke emotions of sorrow and feelings of loss. Thus, the support of the therapist plays a significant role. It is beneficial for this technique to be improvised spontaneously to provide for supportive verbal interventions and for meaningful and manageable flow of images.

Music Listening Techniques

Patients sometimes request to listen to live or recorded music in music therapy to reminisce, reflect, introspect, or refocus attention. Listening to familiar music naturally

stimulates association and builds bridges to memories. This music can take a person immediately back to a certain time and place, the sights, sounds, and often smells of which are imprinted in the memory. Patients often request to hear significant musical selections as ways to reminisce and rebuild connections to transformative events in life, such as relationships with spouses, young children, friends, or parents in early childhood. In advanced stages of illness, there is a focused tendency to reflect on the past, a process that helps resolve unresolved issues and build self-esteem through reflection on accomplishments. This process also can help “make sense” of current predicaments through the introspection on existential meaning and the “purpose” of one's life. Familiar music can stir emotions and conjure feelings of loss and grief. During such reminiscences, the supportive presence of the music therapist can help facilitate. exploration, rebuild communication with significant others, and help patients, when ready, come back to the present with new awareness and insight.

Listening to unfamiliar music is also beneficial. Such music does not necessarily contain the inherent associative attributes that familiar music does. The sounds of new melodies, harmonies, and rhythms can offer opportunities to reflect on inner imagery and help the patient focus on immediate feelings and needs. Unfamiliar music is suggested for use in the management of acute pain due to this potential for engagement without the strong presence of past memories.

The music therapist may improvise melodies and lyrics to reflect mood and medical requirements, i.e., adapting the rhythm of the music to breathing rate and then altering tempo to facilitate improved relaxation or energy flow. The music therapist also can encourage “mindful music listening” (91) as a particular way to benefit from music. This technique combines music with some of the principles set forth by Jon Kabat-Zinn in his mindfulness-based stress reduction methods (92). Patients are encouraged to practice sensory awareness by listening carefully to the instrumentations, paying attention to breath and muscular tension release, and centering themselves in the moment in the music. Such focus can result in a diminution of apprehension and fear as well as a deepened state of relaxation.

Case Example

Michael, age 44, was diagnosed with acute myelogenic leukemia at another hospital in a faraway state. He was not responding to the lengthy chemotherapy treatments there and came to a new hospital for further evaluation and care approximately 2 months after diagnosis. His leukemia was aggressive, and he was fatigued and lethargic. He was referred to music therapy due to his anger, feelings of frustration, and controlling behaviors. He agreed that he would try music therapy due to his “life-long favorite past time of listening to music.”

As the music therapist approached him, he immediately directed her to sit in a chair and listen with him to his favorite compact discs. She did, and listened to him talk at length about the recordings and the memories associated with them. He also stated that he felt very alone and was “trying to keep strong to fight this leukemia.” He asked her to return daily, if possible.

The frequent music therapy sessions were centered on listening to Michael's favorite music. He continued to reminisce at length about his relationships, those that he regretted and those that he treasured. As he listened, he talked about his feelings of dissatisfaction with life's events and his general frustration. Together they listened to recordings of songs that began to reflect and support his verbalizations. The music therapist also sang new songs that articulated some of his thoughts. Michael gradually began to release some of his sorrow and anger as, with the help of the music therapist, he made a “musical journal,” containing titles of songs that depicted significant events in his life. The music therapist taught him “mindful music listening” to use during the nighttime episodes of tension that distressed him. Over time in music therapy, during a 6-month hospitalization before his death, Michael reported improved comfort, exhibited fewer controlling behaviors, and obtained an enhanced sense of self-esteem and self-appreciation.

Listening to music helped this patient achieve a closer view and deepened perspective on the events in his life. The process of reminiscence and the elaboration of feelings associated with memories can assist in the resolving of unfinished business and help patients renew a sense of selfappreciation for personal strengths and accomplishments. Listening to music for Michael, as it can for others, also provided for enhanced relaxation during times of discomfort, anxiety, and insomnia.

Art Therapy

Art therapy interventions in pain management and palliative care are focused on assisting patients in expressing, exploring, and transforming sensations, emotions, and thoughts connected with physical and psychological pain. The art therapist may meet the patient in different settings and offer a variety of therapeutic interventions.

Some patients are seen individually, in the privacy of their hospital room. The art therapist takes a minimum set of art materials, which may consist simply in a block of white paper, a set of colored markers, and a set of oil pastels. Although these bedside interventions are usually brief encounters with the art therapist due to the patient's short length of stay in hospital, they still may be very meaningful for the patient. When the patients are in isolation for bone marrow transplantation, the relationship may become ongoing for the whole time of isolation, and might even continue after discharge.

Other patients are invited to attend an art therapy open studio, in which a group of patients works on individual projects in a quiet, often silent setting, or with suitable music in the background. The open studio, which may be held by the art therapist in the patients' lounge or library, or even in a waiting room, allows patients to drop in and stay as long as they want, according to how they feel at that moment. In the open studio there may be more art material available to stimulate the patients' creativity, and silence is respected to convey a feeling of privacy and safety.

Yet other patients may wish to join an ongoing art therapy group, in which patients meet and interact with each other, often explaining the meaning of their pictures and responding to the images of the other members in the group. The group may be open to new patients every week, or it may be a closed group, with the same patients meeting regularly for a year or longer. A series of art therapy workshops may be offered on specific themes, such as stress management, dreams and fantasies, negative feelings and their transformations, and working towards inner peace. Other art therapy workshops may focus on the patients' free expression and creativity.

Finally, a patient also may be seen individually for shortterm or long-term “art-psychotherapy” to deal with some deeper personal issue or to modify dysfunctional ways of coping with the illness. In this context, the art therapist devotes more time to the verbal interaction with the patient, and to cognitive and psychodynamic interventions, in addition to the symbolic work with the patient's imagery. The therapist may help the patient relate to the imagery, understand it, and explore alternative images.

Five case examples of “brief” art therapy interventions illustrate the varied approaches. These patients were treated in the Department of Psychiatry and Behavioral Sciences at Memorial Sloan Kettering Cancer Center.

Case Example 1: Focusing on the Pain

This patient decided to paint her pain (Fig. 72-1, “The Wound”). This is usually a complex experience, involving concentration on the body, on one level, and on the white page that is outside the body on another level. The patient may experience both the physical pleasure of using colors and shapes, and the psychological positive experience of giving form to something unformed. This combination of factors may increase the capacity to tolerate the pain experience. This patient said that after painting her pain she could “look at it” and “distance herself” from it. Furthermore, in the act of choosing the title for her image, she selected a word that is rather ambiguous (“the wound”), as it may refer to a physical pain and also to a psychological pain, and she liked the ambiguity. The whole experience was relaxing and meaningful for her.

FIGURE 72-1. Focusing on the pain: “The Wound.” (Permission granted and copyright held by Paola Luzzatto, Ph.D.)

Case Example 2: Transforming the Pain

This patient wanted to modify the pain experience through the act of painting (Fig. 72-2, “Turning Pain from Bad to Good”). The kinetic quality of the art therapy experience is used here as a therapeutic factor. The art therapist offered a circular form (called *Mandala*), and the patient filled it with colors he selected, starting from the center and moving towards the outside (the Mandala may be used also with a movement from the outside toward the center, with a different therapeutic aim of feeling “centered”). This patient needed to experience an expansion away from the pain, toward other people and other aspects of his life. Some patients need to reaffirm positive feelings, whereas others need to express the negative ones. This patient experienced a transformation of his pain and entitled his work “from bad to good.”

FIGURE 72-2. Transforming the pain: “Turning Pain from Bad to Good.” (Permission granted and copyright held by Paola Luzzatto, Ph.D.)

Case Example 3: Integrating Negative and Positive

Figure 72-3, “The Mystery of Life and Death,” was made with the simple technique of placing some tempera with a brush in the center of the page, then folding the page, playing with the finger on the paper to spread the paint, then opening up the sheet and finding out what has happened (it is a very simple technique, often used with children in school). One of the main features of this technique is the element of unpredictability and surprise about the final outcome of the picture. The simplicity of the technique did not prevent this patient from developing an image that is quite deep in its meaning. She chose the black tempera, folded the paper, and played with her fingers on the folded paper for quite a while, which was a relaxing movement in itself. She had in mind the theme of “life and death,” and she wanted to end up with an image of some white spaces in between black spaces. The shape that emerged was partly the shape she wanted, but partly a surprise. She said it helped her to give form to her feeling, that death for her was not bad or frightening but was more like that picture: unpredictable, “a mystery.”

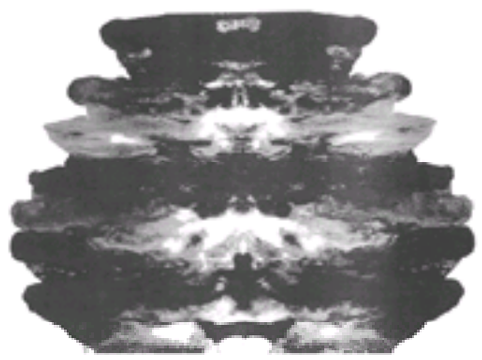

FIGURE 72-3. Integrating negative and positive: “The Mystery of Life and Death.” (Permission granted and copyright held by Paola Luzzatto, Ph.D.)

Case Example 4: Combining Visual and Emotional Processes

Figure 72-4, “Future,” is the result of a long session with a suicidal patient, who was referred by a social worker. The suicidal feeling was first expressed through the choice of the black paper. The patient had been talking and crying with the social worker for a long time, without finding any relief from her despair. Slowly, the patient moved into a different direction, toward a feeling of hope, mainly through the silent relationship with the art materials, within the supportive relationship with the art therapist. This session is an example of how the tool of free association may be important to help a patient to move from a negative to a more accepting state of mind. The patient started with the black paper, then decided to explore her free associations to the color “white”: She imagined “a white blanket” and “a baby under the blanket,” then she imagined “white milk . . . spilled on the kitchen's floor.” Very slowly she moved on to other memories, connections, and fantasies, and ended up with the image of a “white flower” with a yellow center and green leaves. She glued each piece on the black paper. At this point, the patient decided to call this collage “Future”; she told the art therapist that she felt OK, and added the following statement: “I was able to do this, because I was not talking, and therefore I was not crying. I could concentrate, and this happened almost by itself. There is no doubt that something happened, and I feel different about life.” She thanked the art therapist, and she left.

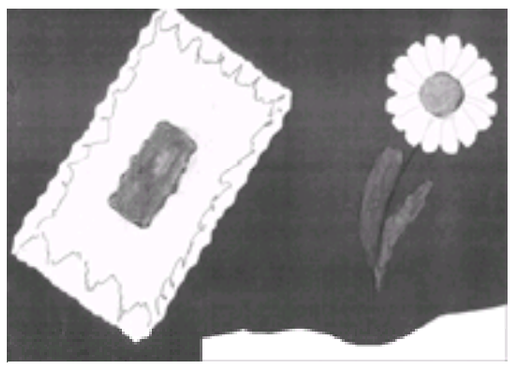

FIGURE 72-4. Combining visual and emotional processes: “Future.” (Permission granted and copyright held by Paola Luzzatto, Ph.D.)

Case Example 5: Responding to Spiritual Needs

Many art therapists find that when the patients are in pain, or they are very weak and cannot sit up on the bed, or cannot hold art material in their hands, it is not possible to have an art therapy session. Nevertheless, apart from the possibility of working with visualization and mental images, the patient who has an image in mind at times may guide the art therapist to “make the image for him/her.” In Figure 72-5, “The Spirit Inside Me,” the patient was shown a preformed body outline, and she told the art therapist how to fill it. She described in detail that she wanted the inside of the body “white” and the outside of the body “blue,” with three flowers on both sides at her feet. Then she wanted some “yellow and orange” outside the circle, and the titles: “The Savior for All” on the top and “The Spirit Inside Me” at the bottom. She was very pleased with the result, and she wanted to hang it in her hospital room. She died a few days after she had made this image, and this picture became an

important legacy for her family.

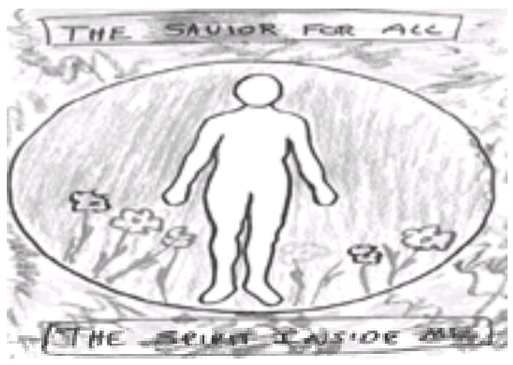

FIGURE 72-5. Responding to spiritual needs: “The Spirit Inside Me.” (Permission granted and copyright held by Paola Luzzatto, Ph.D.)

CONCLUSION

The use of music therapy and art therapy as palliative care interventions requires flexibility and innovation from music therapists and art therapists. New concepts and new interventions are being developed in this field in many countries around the world. Exciting developments are occurring within each of these two disciplines, and cooperation is growing among all creative arts therapies, including movement, poetry, and drama therapies.

The role of the music therapist and of the art therapist within an interdisciplinary team still needs to be clarified, and the specific contributions that these new modalities can offer must be better understood and researched. There are some common misunderstandings: The role of music and art therapists must not be confused with the role of recreational therapists or “arts healers,” who also fulfill essential but different needs. They also must not be seen as providing a specialized activity for musically or artistically talented patients. But where, when, and how are music therapists and art therapists most needed and most helpful in the context of palliative care? Through analysis of the literature and through our own clinical experience in this field, we have come to the conclusion that music and art therapists seem to be particularly effective in three areas: (a) the enhancement of positive feelings of calmness, relaxation, and personal well-being, (b) offering safe cathartic expressions and transformations of sensations and emotions, and (c) facilitating the elaboration of existential and spiritual issues on symbolic and creative levels. On this basis, the inclusion of these two modalities among the interventions offered by a palliative care team could greatly increase its effectiveness.

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COMPLEMENTARY AND ALTERNATIVE APPROACHES

BARRIE R. CASSILETH

A vast collection of disparate approaches, from unproved cancer cures to soothing, adjunctive regimens, is subsumed under the single umbrella term “complementary and alternative medicine,” known commonly by the acronym “CAM.” Although they are typically discussed in the aggregate, it is clinically and conceptually necessary to distinguish between the two categories because they comprise profoundly different modalities.

Alternative therapies generally may be perceived literally as such; they are promoted as cancer treatments and sometimes as cancer cures, and are often sold for use instead of mainstream therapy. By definition, alternative therapies are unproved. If they were backed by solid data, they would not be “alternative.” Rather, they would be found in every oncology program and used as viable cancer treatments.

Alternative regimens, which are typically invasive and biologically active, are usually very expensive and potentially harmful. They may harm directly through physiologic activity, or indirectly when patients postpone receipt of mainstream care. Late-stage patients are especially vulnerable to these therapies, as they often promise cure of even advanced disease.

Complementary therapies, in contrast, are used for symptom management and to enhance well-being. They serve as adjuncts to mainstream care; promoted not as cancer cures, but as means of enhancing patients' quality of life. Complementary therapies are supportive, palliative care in every respect. They address body, mind, and spirit, aiming to control pain and other symptoms and to optimize quality of life for patients and families. This definition is essentially identical to that proposed by the World Health Organization for palliative care (1).

In CAM, therefore, we must work with two poles of a continuum. Patients need the knowledge and support to forego the siren calls to seek metabolic therapies in Tijuana; to buy shark cartilage; to self-treat with high-dose vitamins and other products sold over the counter or delivered intravenously in alternative clinics; and to seek remission of disease through self-proclaimed healers, electromagnetic cures, and many other products and approaches.

At the same time, patients need access to the comfort of supportive complementary modalities. These therapies are becoming increasingly available not only directly to patients on a private basis, but also in hospitals, clinics, and homes as part of symptom control and the general effort to ease the physical, psychosocial, and spiritual distresses associated with cancer and especially with end-stage disease.

This chapter addresses the state of CAM in the larger health care system, and reviews the alternative therapies that are so widely and temptingly available to patients and families. Physicians and other caregivers need to know about these pervasive alternatives. Helpful complementary therapies are reviewed as the conclusion to this chapter.

IMPACT OF COMPLEMENTARY AND ALTERNATIVE MEDICINE ON THE HEALTH CARE SYSTEM

The acceptance of unconventional therapies, along with the advent of managed care, advances in biotechnology, and other significant medical and societal events, marked health care in the 1990s and was among the significant changes that occurred during that time. The popularity of CAM has affected every component of the health care system and all specialties of medicine, including palliative oncologic care. It has left its mark on the thinking and practice of physicians and other health professionals, and broadened patients' involvement and influence in their own care.

No longer a collection of covert practices (2), unconventional cancer medicine today is highly visible, and information about it is widely available to the general public. It is a multibillion dollar business in the United States, and of equivalent impact and importance throughout the developed world.

Internationally as well as in North America, the use of CAM for cancer is widespread. A systematic review (3) located 26 surveys of cancer patients from 13 countries, including five from the United States. The average prevalence of CAM use across all studies was 31%. Therapies most commonly adopted around the world included dietary treatments, herbs, homeopathy, hypnotherapy, imagery or visualization, meditation, megavitamins, relaxation, and spiritual healing. New investigations substantiate these results (4,5 and 6).

All but one of the United States surveys obtained information about specific therapies employed. Patients used Laetrile, metabolic therapies, diets, spiritual healing, megavitamins, imagery, and “immune system stimulants” (3). Across samples, the prevalence of CAM use in the United States ranged from 7% to 50%.

Additional surveys involving members of the U.S. general public (not cancer patients) uncovered prevalence rates of one-third in a representative sample of 1539 adults as reported in 1993 (7). Two surveys published in 1997 report prevalence rates of 50% of 113 family practice patients (8) and 42% of 1500 members of the general public (9). A 1998 publication reports that 42% of 2055 people surveyed used CAM (10). A large, 1999 survey of over 24,000 individuals found 8% use of CAM, with or without mainstream care (11).

Prevalence rates from all CAM studies, conducted in the United States and internationally, vary from less than 10% to more than 50%. This broad range, with its apparent discrepancies, may be attributed primarily to variable understandings and definitions of CAM. Surveys often do not define CAM, or more typically, define it extremely broadly, resulting in the inclusion of lifestyle activities such as weight loss efforts, exercise, church attendance, and support activities such as group counseling, thus resulting in bloated figures for CAM use. Moreover, few studies distinguish between use of alternative therapies (in lieu of mainstream cancer treatment) versus adjunctive use of complementary modalities.

Although research evidence is scanty (2), it appears that approximately 8–10% of tissue-biopsy diagnosed cancer patients eschew mainstream therapy and immediately seek alternative care. The vast majority of CAM users, however, seek complementary, not alternative, therapies for cancer.

The profound influence of 1994 legislation allowing herbal medicines and other “food supplements” to be sold over the counter without U.S. Food and Drug Administration (FDA) review is evident in the increased use of herbal remedies from 3% in 1991 to 17% in 1997 (11). It is estimated that sales of dietary supplements more than doubled in the 6 years since passage of the 1994 law. However, herbal supplements sales began to decline in 1998, growing just 12% that year, and sales grew only 1% in 2000 (12). The decline is presumed to be due to several factors, including unrealistically high public expectations, media reports about safety concerns

and questionable effectiveness, and public confusion about the vast array of products (12).

Virtually all studies conducted to date of cancer patients and of the general public internationally show that those who seek CAM therapies tend to be female, better educated, of higher socioeconomic status, and younger than those who do not. They tend to be more health conscious and to use more mainstream medical services than do people who do not use CAM. Despite the drop in sales of herbal remedies, there is indication of a growth in CAM use by cancer patients in recent years (3); a secondary analysis of close to 3000 cancer patients estimates a 64% increase after 1987 (13). It is likely that this reflects expanded use and variety of over-the-counter remedies and broader availability of complementary therapies in mainstream cancer programs and centers.

Complementary and Alternative Medicine Use among Pediatric Cancer Patients

The use of CAM methods among pediatric oncology patients represents a special and understudied issue. Surveys in Australia and Finland (3), in British Columbia (6), and in the Netherlands (14) indicate substantial interest in CAM, especially in more recent years, with 40–50% of pediatric oncology patients in those countries receiving alternative or complementary therapies.

Few studies of CAM use among U.S. pediatric oncology patients have been published in the past 10 years (15). A 1998 article reported that 65% of 81 U.S. cancer patients used CAM, whereas 51% of 80 control-group children receiving routine checkups did so. Of particular interest is the type of CAM received. Prayer, exercise, and spiritual healing accounted for more than 96% of CAM used. Excluded from this sample by definition, however, were the pediatric patients brought for alternative treatment to clinics in the United States, Mexico, or elsewhere. Patients who received only alternative cancer therapies did not appear in CAM surveys, because all but one such survey were conducted in mainstream clinics or hospitals.

Public Access to Information

CAM today is very much an open and public issue, discussed widely in the media and readily found on the Internet. Magazines and television specials provide the general public with details about new CAM therapies. The yellow pages of telephone books in most cities and towns typically list various types of CAM practitioners.

Information available to the public varies widely in accuracy. Many Web sites and publications that appear to be objective actually are sponsored by commercial enterprises that promote and sell the products they report. Misinformation about health issues is widespread. In 1999, the U.S. Federal Trade Commission (FTC) announced that it had identified hundreds of Web sites promoting and selling phony cures for cancer and other serious ailments among the estimated 15,000–17,000 health-related Web sites (16).

In 2001, the FTC told six companies to stop making false health claims, including the claim that mild electric currents kill parasites that “cause” cancer and Alzheimer's, and that herbs should be used to treat cancer instead of conventional treatments such as surgery and chemotherapy (17).

This is part of the FTC's “Operation Cure All,” an effort to stop bogus Internet health claims (18). The U.S. Department of Health and Human Services released a report expressing concern about the lack of information to enable consumers to properly evaluate the credibility of Internet health information (19).

Recognition by Mainstream Journals and Physicians

A survey of 295 family physicians in the Maryland-Virginia region (20) revealed that up to 90% view complementary therapies such as diet and exercise, behavioral medicine, and hypnotherapy as legitimate medical practices. A majority refers patients to nonphysicians for these therapies or provides the services themselves. Homeopathy, Native American medicine, and traditional Oriental medicine were not seen as legitimate practices.

Two hundred Canadian general practitioners held similar views, noting their patients' interest especially in chiropractic. These physicians perceive chiropractic care, hypnosis, and acupuncture for chronic pain as the most effective CAM therapies, and homeopathy and reflexology as less efficacious (21). A meta-analysis of 12 studies in Great Britain suggests that British physicians view complementary medicine as only moderately effective (22), a level of enthusiasm that contrasts with the fervent efforts of the British Royal Family to promote homeopathy and other complementary therapies, and to merge them with mainstream care.

In addition to increasing coverage of CAM services by health insurers, a final marker of mainstream interest noted here is the publication of CAM research articles in major mainstream medical journals. Articles about CAM in major journals shifted from commentaries through the 1970s expressing realistic concern about quackery (e.g., 23–25), to surveys of patients' knowledge and use of unproven methods in the 1980s (e.g., 26–28), to reports of actual research results starting primarily in the mid-1990s.

The *Journal of the American Medical Association*, the *New England Journal of Medicine*, the *Lancet*, the *British Medical Journal*, and specialty journals such as *Cancer* and the *Journal of Clinical Oncology* have published reports of CAM research in recent years. In 1996–1997, the National Library of Medicine added many new CAM search terms to its medical subject headings, and began to cover alternative medicine journals previously not reviewed for inclusion in Medline.

However, not all mainstream physicians are pleased with CAM, with current efforts to integrate CAM and mainstream medicine, or with a separate National Institutes of Health research entity for CAM (29,30 and 31).

COMPLEMENTARY AND ALTERNATIVE MEDICINE THERAPIES AND PRACTITIONERS

CAM therapies may be categorized in a variety of ways. The seven categories noted here were developed by the Office of Alternative Medicine (32), now the National Center for Complementary and Alternative Medicine: diet and nutrition; mind-body techniques; bioelectromagnetics; alternative medical systems; pharmacological and biological treatments; manual healing methods; and herbal medicine. Currently popular therapies are discussed within each of these categories. Most of these approaches are unproved methods promoted as alternatives to mainstream cancer treatment. Helpful complementary or adjunctive therapies are discussed separately at the end of this chapter.

Diet and Nutrition

Advocates of dietary cancer treatments typically extend mainstream assumptions about the protective effects of fruits, vegetables, fiber, and avoidance of excessive dietary fat in reducing cancer risk, to the idea that food or vitamins can cure cancer. Proponents of this belief make their claims in books with titles such as *The Food Pharmacy: Dramatic New Evidence that Food is your Best Medicine*, *Prescription for Nutritional Healing*, and *New Choices in Natural Healing*.

The macrobiotic diet is a persistently popular example of such dietary approaches. As currently constructed, it is similar to recent U.S. Department of Agriculture dietary pyramid recommendations for healthful eating, except that the macrobiotic diet omits dairy products and meat. This diet derives 50–60% of its calories from whole grains, 25–30% from vegetables, and the remainder from beans, seaweed, and soups. All animal meat and certain vegetables and processed foods are to be avoided, and soybean consumption is promoted. Despite claims in publications and Web sites, there is no evidence that the macrobiotic diet can cure or is beneficial for patients with cancer. Moreover, this diet may be nutritionally deficient and can cause problematic weight loss, especially in patients with advanced cancer.

Metabolic Therapies and Detoxification

Metabolic therapies continue to draw patients from North America to the many clinics in Tijuana, Mexico. These therapies involve practitioner-specific combinations of diet plus vitamins, minerals, enzymes, and “detoxification.” One of the best known sites for metabolic therapy is the Gerson clinic, where treatment is based on the belief that toxic products of cancer cells accumulate in the liver, leading to liver failure and death. The Gerson treatment aims to counteract liver damage with a low-salt, high-potassium diet, coffee enemas, and a gallon of fruit and vegetable juice daily (33). The clinic's use of liquefied raw calf liver injections was suspended in 1997, after sepsis in a number of patients.

Other Tijuana clinics and practitioners provide their own versions of metabolic therapy, each applying an individualized dietary and “detoxification” regimen. Additional components of treatment are included according to practitioners' preferences. Metabolic regimens are based on belief in the importance of “detoxification,” which is thought necessary for the body to heal itself. Practitioners view cancer and other illnesses as symptoms of the accumulation of toxins. This is a nonphysiologic but venerable concept that originated in ancient Egyptian, Ayurvedic, and other early efforts to understand illness and death, both of which were believed caused by the putrefaction of food in the colon. Decay and purging were major themes in early cultures' therapeutic regimens. Neither the existence of toxins nor the benefit of colonic cleansing has been documented.

Modern variations on the older approach to internal cleansing are drinkable cleansing formulas, said to detoxify and rejuvenate the body. Many variations are available

in health food stores, books, and on the Internet. A shake of liquid clay, psyllium seed husks, and fruit juice, for example, is said to remove harmful food chemicals and air pollutants (34). These products tend to function as major laxatives, potentially dangerous when taken over days or weeks or on a regular basis as recommended by promoters, and of special concern for cancer patients.

Megavitamin and Orthomolecular Therapy

Some patients and alternative practitioners believe that large dosages of vitamins—typically hundreds of pills a day—or intravenous infusions of high-dose vitamin C can cure disease. In 1968, Nobel Laureate Linus Pauling coined the term “orthomolecular” to describe the treatment of disease with large quantities of nutrients. His claims that massive doses of vitamin C could cure cancer were disproved in clinical trials (35,36), but megavitamin and orthomolecular therapy—the latter adds minerals and other nutrients— remain popular among cancer patients. There is no evidence that megavitamin or orthomolecular therapy is effective in treating any disorder.

Mind-Body Techniques

The potential to influence health with our minds is an extremely appealing concept in the United States. It affirms the power of the individual, a belief intrinsic to U.S. culture. Some mind-body interventions have moved from the category of alternative, unconventional therapies into mainstream complementary or supportive care. Good documentation exists, for example, for the effectiveness of meditation, biofeedback, and yoga in stress reduction and the control of some physiologic reactions (37,38).

The argument that patients can use mental attributes or mind-body work to cure cancer is not tenable (39,40). Attending to the psychological health of cancer patients is a fundamental component of good cancer care. Support groups, good doctor-patient relationships, and the emotional and instrumental help of family and friends are vital. However, the idea that patients can influence the course of their disease through mental or emotional work is not substantiated and can evoke feelings of guilt and inadequacy when disease continues to advance despite patients' best spiritual or mental efforts (41).

Bioelectromagnetics

Bioelectromagnetics is the study of interactions between living organisms and their electromagnetic fields. According to proponents, magnetic fields penetrate the body and heal damaged tissues, including cancers (42). No peerreviewed publications could be located for this work, or for any clinical cancer-related claims regarding bioelectromagnetics. Despite the lack of data and the patent absurdity of these claims, proponents continue to sell electromagnetic therapy as a cure for cancer and other major illnesses (17,43).

Electromagnetic therapy and the related group of energy therapies, discussed in the section Manual Healing Methods, illustrate a striking difference between previous and currently popular alternative practices. Whereas many earlier alternatives reflected concepts important to scientific study of the time, many of today's popular alternatives are mystical and explicitly contrary to contemporary scientific and medical thought. It is as though the new millennium encouraged deeper adoption of explanatory notions applied in millennia past.

Alternative Medical Systems

This category includes ancient systems of healing typically based on concepts of human physiology that differ from those accepted by modern Western science. Two of the most popular healing systems are traditional Chinese medicine and India's Ayurvedic medicine, popularized by bestselling author Deepak Chopra, MD (44).

“Ayurveda” comes from the Sanskrit words “ayur” (life) and “veda” (knowledge). Ayurveda's ancient healing techniques are based on the classification of people into one of three predominant body types. There are specific remedies for disease, and regimens to promote health, for each body type. This medical system has a strong mind-body component, stressing the need to keep consciousness in balance. It uses techniques such as yoga and meditation to do so. Ayurveda also emphasizes regular detoxification and cleansing through all bodily orifices.

Traditional Chinese medicine explains the body in terms of its relationship to the environment and the cosmos. Concepts of human physiology and disease are interwoven with geographic features of ancient China and with the forces of nature. Chi, the life force said to run through all of nature, flows in the human body through vertical energy channels known as meridians.

The 12 main meridians are believed to be dotted with acupoints. Each acupoint corresponds to a specific body organ or system, so that needling or pressing the acupoint can redress the life-force imbalance causing the problem in that particular organ. To determine the source of the blockage, the practitioner relies on pulse diagnosis, a technique applied by doctors of traditional Chinese medicine today as it was millennia ago. It involves concentration on several body pulses by the practitioner for approximately 45 minutes.

Although the very existence of chi or a “vital energy force” remains unproved, tai chi is a well-documented, effective, gentle exercise technique, particularly useful in preventing falls among the frail or elderly (45,46 and 47).

Traditional Chinese medicine also includes a full herbal pharmacopoeia with remedies for most ailments, including cancer (48). Chinese herbal teas and relaxation techniques are soothing and appealing to many patients with cancer, who use them as complementary therapies. The potential anticancer benefits of many Chinese herbal compounds and other botanicals are under investigation in the United States and elsewhere.

Pharmacological and Biological Treatments

Because pharmacological and biological alternative treatments are invasive and biologically active, they are highly controversial. Probably the best known and most popular pharmacological therapy today is antineoplastons, developed by Stanislaw Burzynski, MD, PhD, and available in his clinic in Houston, Texas (49). Laboratory analysis conducted by a respected scientist concluded that antineoplastons did not normalize tumor cells (50).

Promising anecdotal reports encouraged a clinical trial for pediatric patients with brain tumors, but a National Cancer Institute research effort failed to accrue patients. Further research at the Burzynski Institute was permitted under an investigational new drug (IND), but preliminary data were criticized as uninterpretable, and the therapy as useless and toxic, by respected mainstream scientists (51). Burzynski and his patients continue the antineoplaston therapy and remain vocal advocates of its efficacy.

Immunoaugmentive therapy (IAT) was developed by the late Lawrence Burton, PhD, and offered in his clinic in the Bahamas. Injected IAT is said to balance four protein components in the blood and to strengthen the patient's immune system. Burton claimed that IAT was particularly effective in treating mesothelioma. Documentation of IAT's efficacy remains anecdotal. The clinic has continued to operate after Burton's death, but its popularity seems to have waned (52).

Interest in shark cartilage as a cancer therapy was activated by a 1992 book by I. William Lane, PhD, *Sharks Don't Get Cancer*, and by a television special that displayed apparent remissions in patients treated with shark cartilage in Cuba. The televised outcome was strongly disputed by oncologists in the United States. Advocates base their therapy on its putative antiangiogenic properties, but the shark cartilage protein molecules are too large to be absorbed by the gut and would be destroyed even if absorbed. Shark cartilage actually decomposes into inert ingredients and is excreted. A recent phase I–II trial of shark cartilage found no clinical benefit (53).

Cancell is another biological remedy that appears to be especially popular in Florida and the Midwestern United States. Proponents claim that it returns cancer cells to a “primitive state” from which they can be digested and rendered inert. FDA laboratory studies, which showed Cancell to be composed of common chemicals, including nitric acid, sodium sulfite, potassium hydroxide, sulfuric acid, and catechol, found no basis for proponent claims of Cancell's effectiveness against cancer (54).

Laetrile, an illegal and documented useless product long thought banished (55), was only dormant. It returned in the year 2000, readily available on the Internet.

Manual Healing Methods

Osteopathic and chiropractic doctors were among the earliest groups to use manual methods. Today, there are numerous approaches involving touch and manipulation technique, including hands-on massage. The benefit of chiropractic treatment of low back pain was supported by a National Institutes of Health

consensus conference (56), but its value is widely disputed by mainstream physicians (57).

One of the most popular manual healing methods is therapeutic touch (TT), which, despite its name, involves no direct contact. In TT, healers move their hands a few inches above a patient's body and sweep away “blockages” to the patient's energy field. Although a study in the *Journal of the American Medical Association* showed that experienced TT practitioners were unable to detect the investigator's “energy field” (58), and despite mainstream scientists' unwillingness to accept its fundamental premises, TT is taught in North American nursing schools and widely practiced by nurses in the United States and other countries (59).

Related to TT are several therapies that involve manipulation of a putative human energy field, or use of an individual's special gift for energy healing. Healing of this type, which has remained popular over the centuries in less developed areas of the world (60,61), has gained increasing public interest and acceptance in the United States. Healers in many areas of the United States claim the ability to cure people of cancer. Although they may cause only minor difficulties when patients also receive mainstream care, many patients are firmly convinced of healers' abilities and decline even to have tumors removed surgically in favor of healers' ministrations.

A large advertisement in the *New York Times* (July, 1999) and its companion Web site claim the ability of a Dr. Yan Xin to emit healing qi (chi). The charge is $3.5 million to cure a fatal disease, and $5000 for stress release, weight reduction, or “other health improvements” (62).

Herbal Treatments for Cancer

Herbal remedies typically are part of traditional and folk healing methods with long histories of use. Herbal medicine is found is most areas of the world and across all cultures historically. Although many herbal remedies are claimed to have anticancer effects, only a few have gained substantial popularity as alternative cancer therapies.

For decades, Essiac has remained a popular herbal cancer alternative in North America. Developed initially by a Native healer from Southwestern Canada, it was popularized by a Canadian nurse, Rene Caisse (Essiac is Caisse spelled backwards). Essiac is comprised of four herbs: burdock, turkey rhubarb, sorrel, and slippery elm. Researchers at the National Cancer Institute and elsewhere found that it has no anticancer effect. Essiac is illegal in Canada (32), but it is widely available in the United States.

Iscador, a derivative of mistletoe, is a popular cancer remedy in Europe, where it is said to have been in continuous use as folk treatment since the Druids. It is used in many mainstream European cancer clinics, typically in conjunction with chemotherapy. Despite many studies, definitive data in support of the usefulness of Iscador have not emerged.

Herbal Remedies

Cancer patients use many over-the-counter herbal products in addition to or instead of those promoted specifically as cancer treatments. It is therefore important to recognize herbal remedies that are toxic or tend to interact with other medications as well as those that may help cancer patients. Because neither the FDA nor any other agency examines herbal remedies for safety and effectiveness, few products have been formally tested for side effects or quality control, but information is beginning to emerge on the basis of public experience with over-the-counter supplements.

Reports in the literature describe severe liver and kidney damage from some herbal remedies. These reports underscore the fact that “natural” products, contrary to apparent consumer belief, are not necessarily safe or harmless (63). Most members of the public apparently are not aware that herbs are essentially dilute natural drugs that contain scores of different chemicals, most of which have not been documented. Effects are not always predictable.

Moreover, the potential for herb-drug interaction is sufficiently problematic that patients on chemotherapy or other major medications should not use herbal remedies. Similar cautions are necessary for patients receiving radiation, as some herbs photosensitize the skin and cause severe reactions. Some herbs interfere with coagulation and produce dangerous blood pressure swings and other unwanted interactions with anesthetics (64). Herbs such as feverfew, garlic, ginger, and ginkgo have anticoagulant effects and should be avoided by patients on warfarin sodium (Coumadin), heparin sodium, aspirin, and related agents. The risk of herb-drug interactions appears to be greatest for patients with kidney or liver problems.

The California Department of Health found unsafe levels of mercury and other toxic metals in more than a third of Asian patent medicines studied. Several instances of heart problems resulting from digitalis-contaminated supplements have been reported (e.g., 65). Concerns have been raised even about dietary antioxidants, which may interact with chemotherapeutic agents (66).

Regulatory and Safety IssuesM

Dietary supplements, which include vitamins and minerals, homeopathic remedies, herbal treatments, antioxidants, and other over-the-counter products, are probably the most popular unconventional remedies used today by cancer patients, as well as by the public in general. According to *Nutrition Business Journa*l, 1998 sales of supplements sold over the Internet alone reached $40 million, an increase from $12 million in 1997. *Nutrition Business Journal* estimates sales of food supplements at $160 million for 1999 and $500 million in 2001.

No legal standards exist for the processing or packaging of herbs. Quality-control standards and reviews are needed. Because they are not mandatory, however, few food supplement companies voluntarily self-impose quality evaluation and control. Consumer protection and enforcement agencies cannot provide protection against contaminated or falsely advertised products. Current federal regulations do not permit such oversight, and regulatory capability would prohibit full analysis and ongoing oversight of the estimated 20,000 food supplement items now sold over the counter.

The magnitude and seriousness of the problem hopefully will result in the establishment of government oversight programs of some kind, despite anticipated efforts on the part of the food supplement industry to block efforts that could lead to regulation.

COMPLEMENTARY THERAPIES

Complementary therapies are safe, nontoxic, noninvasive, easy to use, and inexpensive. Many may be self-managed, meaning that practitioners often are unnecessary, which gives patients the rare and important opportunity to maintain a measure of control over their well-being. Supportive or complementary modalities also are soothing, comforting, and distracting, and are backed by good efficacy data.

Some complementary therapies, such as relaxing in a warm bath or painting soothing mental pictures, are intuitively comforting and helpful. Major supportive therapies have been singled out for more detailed review. These therapies—music therapy, therapeutic massage, acupuncture, and mind-body modalities—address some of the most pervasive and difficult problems faced by patients under palliative care. Although data do not always come from the patient population of concern to us here, research shows that these minimally invasive, side effect–free therapies effectively reduce anxiety, depression, pain, dyspnea, nausea, and fatigue.

Music Therapy

Music therapy is provided by professional musicians who are also trained music therapists. They often hold professional degrees in music therapy, and are adept in dealing with the psychosocial as well as clinical issues faced by patients and family members.

Music therapy is particularly effective in the palliative care setting. Formal music therapy programs in palliative medicine exist in several major institutions, including the Memorial Sloan-Kettering Cancer Center and the Cleveland Clinic (67). Although music therapy extends back to folklore and Greek mythology (Apollo was the god of both music and medicine), it has been studied scientifically only in recent years.

Controlled trials indicate that music therapy produces emotional and physiologic benefits, reducing anxiety, stress, depression, and pain. Music intervention significantly reduced heart rate, respiratory rate, and anxiety scores among inpatients after myocardial infarction (68), ventilatory assistance (69), and patients undergoing flexible sigmoidoscopy (70). Live versus recorded music more effectively reduced anxiety (71).

In the preoperative setting, randomized trials found that music reduced anxiety and its physiologic correlates such as blood pressure (72,73 and 74) and salivary cortisol, a biochemical marker of stress and anxiety (75). Music lowered blood pressure and anxiety scores during and after eye surgery (76) and among women undergoing hysterectomies in a randomized, controlled trial (77).

Music therapy was shown to be effective against laboratoryinduced pain (78), among cancer outpatients (79), and among cancer patients with chronic pain (80). Music reduced intraoperative analgesic requirements compared to controls (81), and patients randomized to a music intervention reported significantly less pain and required less pain medication (82,83). In what was possibly the largest trial of its type, 500 surgical patients were randomized to control, recorded music, jaw relaxation, or a music/jaw relaxation combination. Music led to significant decreases in both pain intensity and related distress associated with pain (83,84 and 85). Music also can help reduce depression (86,87,88 and 89).

Massage Therapy

The benefits of massage therapy are documented for end-of-life populations (90,91 and 92), and the pain-reducing effects of this intervention are well documented for cancer patients at various stages of illness (93,94 and 95). In the largest study to date, 87 hospitalized cancer patients were randomized to foot massage (also called reflexology) or to control on a crossover basis. Pain and anxiety scores fell with massage, with differences between groups achieving substantial significance *(p* = .001) (95).

Pain scores fell by two-thirds immediately after the first massage of patients with postburn itching and pain, and improvements appeared to be cumulative. No similar changes were seen in controls (96). Other studies found similar results for burn patients (97) and patients with postoperative pain (98).

Acupuncture

Several randomized, controlled trials have examined acupuncture for dyspnea. A laboratory-based model of methacholine-induced bronchospasm, which was a blinded, placebo-controlled, randomized investigation, allowed good experimental control. Significant differences in lung function emerged between needling true versus inactive (“sham”) points for airway conductance, forced expiratory volume, and forced expiratory flow (99).

A similarly controlled study in a laboratory setting involved asthmatic children. Exercise-induced reductions in forced expiratory volume, peak expiratory flow rate, and forced vital capacity were significantly lower in real compared to sham acupuncture (100). A trial of acupressure for chronic obstructive pulmonary disorder also found significant differences between groups for subjective breathlessness (101). Only one trial has been reported in cancer. Although uncontrolled, the results are provocative. Twenty patients in palliative care received a single session of acupuncture. A 43% reduction in breathlessness after 10 minutes of needle insertion was found, and it was maintained at 6-hour follow-up (102).

Cancer-related fatigue is a highly distressing and common symptom for which there is no known effective treatment. Published case reports include fatigue associated with multiple sclerosis (103) and chronic fatigue syndrome (104,105). One randomized trial of acupuncture in which fatigue was an end point has been published (106). Although this trial was very small (13 patients) and the acupuncture prescription used was for the treatment of pain and nausea rather than fatigue, patients receiving acupuncture experienced approximately a 15% reduction in fatigue scores; the mean change among controls was zero. Anecdotal information has been obtained from the acupuncturists and patients in the Memorial Sloan-Kettering Cancer Center Integrative Medicine Service. Several cancer patients scoring 5 or higher on a 10-point scale experienced clinically important reductions in fatigue after acupuncture treatment.

Meta-analyses and systematic reviews of acupuncture for pain support its usefulness for dental and back pain (107,108). An uncontrolled report of acupuncture for pain in hospice patients indicates that 62% had a good or excellent response (109). A systematic review (110), as well as a pilot study (111), indicates that acupuncture effectively reduces nausea. In a study of 183 cancer patients, almost half experienced decreased pain after acupuncture (112).

Mind-Body Therapies

The varied group of mind-body therapies is geared to decrease stress and promote relaxation in different ways. Hypnotherapy has been shown to reduce chemotherapyrelated nausea and vomiting in children (113), and possibly to control anxiety and nausea (114). Hypnosis for pain is well supported (115,37). Other techniques, including visualization and progressive relaxation, also decrease pain and promote well-being (116,117).

Other complementary therapies, such as spiritual care, counseling, and group support, have been part of supportive and palliative care in cancer for decades. The complementary therapies discussed here represent an extension of those efforts to decrease symptoms and enhance patients' quality of life. Our challenge is to help patients avoid the pitfalls of useless unproved therapies, while ensuring their access to the safe, noninvasive, beneficial complementary modalities reviewed here (118).

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LONG-TERM SURVIVORSHIP: LATE EFFECTS

NOREEN M. AZIZ

Owing, in part, to tremendous strides in disease treatment, cancer survivors are living for extended periods beyond their initial diagnoses, often with various physical and psychosocial sequelae. Conceptually, cancer is increasingly being considered a chronic disease for the individuals diagnosed with it, and for their families. Questions of particular importance to cancer survivors include surveillance for the adverse sequelae, or late effects, of treatment, and the development of new cancers. These questions not only occupy a central core of importance in and of themselves, but also have the potential to impact on infrastructure systems such as databases, follow-up requirements for clinical trials, new therapeutic approaches, dosages of chemotherapeutic drugs, surveillance recommendations, and the cancer research agenda itself.

Statistical trends show that, in the absence of other competing causes of death, 59% of adults diagnosed with cancer today can expect to be alive in 5 years. Estimated 5-year survival rates for those diagnosed during childhood (< age 19) are even higher, with almost 75% of childhood cancer survivors estimated to be alive at 5 years and 70% at 10 years. Prevalence proportions estimated from cancer incidence and follow-up data in the Surveillance, Epidemiology, and End Results registry indicate that there are currently 8.9 million cancer survivors in the United States, representing approximately 3.3% of the entire U.S. population (1).

These dramatic strides in survival over the past three decades are the result of advances in early detection, adjuvant and other aggressive therapeutic strategies, and the widespread use of combined modality therapy (surgery, chemotherapy, and radiotherapy). Cancers such as testicular cancer, acute lymphoblastic leukemia (ALL), and Hodgkin's disease are now considered amenable to cure. Patients with many common cancers, such as breast and colorectal, can look forward to a vastly improved disease-free and overall survival, and patients with potentially incurable disease can look forward to living for extended periods as a result of better disease control (2,3 and 4).

These benefits of antineoplastic therapy are balanced by a spectrum of late complications, which range from minor and treatable to serious and, occasionally, potentially lethal (5). One-fourth of late deaths occurring among pediatric cancer survivors during the extended survivorship period, when the chances of primary disease recurrence are negligible, can be attributed to a treatment-related effect such as a second cancer or cardiac dysfunction. The most frequently observed sequelae include endocrine complications, growth hormone deficiency, primary hypothyroidism, and primary ovarian failure (6). Also included within the rubric of late effects are second malignant neoplasms arising as a result of genetic predisposition (e.g., familial cancer syndromes) or the mutagenic effects of therapy. These factors may act independently or synergistically. Synergistic effects of mutagenic agents such as cigarette smoke, or toxins such as alcohol, are largely unknown.

This chapter discusses both late and long-term effects. The discussion includes (a) relevant definitional issues, (b) generalizations about long-term and late effects, (c) issues unique to certain cancer sites, (d) special considerations when primary diagnosis and treatment occurs during childhood or various stages of adulthood, (e) a review of late and long-term sequelae by organ system or tissue affected, (f) second malignant neoplasms, (g) ancillary sequelae, and (h) follow-up care for late and long-term effects.

DEFINITIONAL ISSUES

“Cancer survivorship” was first described by Fitzhugh Mullan, a physician who had been diagnosed with cancer himself (7). His earlier definition coincides with the widely accepted one today: “everyone diagnosed as having cancer, beginning from the point of diagnosis to the end of life, is a cancer survivor.” Mullan described the survivorship experience by equating it with the climatic seasons of the year. He recognized three “seasons” or phases of survival: (a) *acute* (extending from diagnosis to the completion of initial treatment; issues dominated by treatment and its side effects); (b) *extended* (beginning with the completion of initial treatment for the primary disease or remission of disease; dominated by watchful waiting, regular follow-up examinations, and intermittent therapy); and, (c) *permanent* survival (not a single moment in time—evolves from extended diseasefree survival when the likelihood of recurrence is sufficiently low). An understanding of these phases of survival is important vis-à-vis the recognition and optimal management of late effects of treatment.

The physiological sequelae of cancer and its treatment incorporate two related areas: (a) *long-term physiological effects* (chronic physiological sequelae persisting beyond the acute cancer treatment phase), and (b) *late effects* (delayed physiological sequelae occurring months to years after treatment). Physiological sequelae can further be classified as (a) *system-specific* (e.g., organ damage, failure, or premature aging; immunosuppression or compromised immune systems; and endocrine damage); (b) *second malignant neoplasms* (e.g., an increased risk of recurrent malignancy, increased risk of a certain cancer associated with the primary malignancy, or increased risk of secondary malignancies associated with cytotoxic or radiologic cancer therapies); and (c) *functional changes* (e.g., lymphedema, incontinence, pain syndromes, neuropathies, fatigue), *cosmetic* changes (e.g., amputations, ostomies, and skin/hair alterations), and *comorbidities* (e.g., osteoporosis, arthritis, and hypertension).

Late effects of cancer treatment occur because effects of therapy on organs or tissues may become manifest only with time or because there is unmasking of hitherto unseen injury to immature organs by developmental processes (3). Any side effect for which a cancer patient must compensate during life is a long-term, or persistent, effect. Because tissue damage noted during or at the end of therapy may remain stable or become progressive, late effects refer specifically to unrecognized toxicities that are absent or subclinical at the end of therapy but manifest later as a result of growth, development, increased demand, or aging. Compensatory mechanisms that initially maintain the function of injured organs may fail over time or with organ senescence. Persistent symptoms differ from late effects of treatment as they begin during treatment and continue after treatment, rather than appearing months to years after the completion of treatment (8). Some researchers classify cognitive problems, fatigue, lymphedema, and peripheral neuropathy as persistent symptoms. Patients demonstrating signs or symptoms of late or long-term effects may have to undergo major lifestyle adjustments for which they are unprepared (9,10,11 and 12).

GENERALIZATIONS ABOUT LATE EFFECTS

It is now possible to anticipate certain types of late effects on the basis of specific therapies the survivor was exposed to, the age of the survivor at the time of treatment, combinations of treatment modalities used, and the dosage administered. There are differences in susceptibility between pediatric and adult patients. Generally, chemotherapy results in acute toxicities that can persist, whereas radiation leads to sequelae that are not apparent immediately and surface after a latent

period. Combinations of chemotherapy and radiation therapy are more often associated with late effects in the survivorship period.

Toxicities related to chemotherapy, especially those of an acute but possibly persistent nature, may be related to proliferation kinetics of individual cell populations, as these drugs are usually cell cycle dependent. Thus, organs or tissues most susceptible are those with high cell proliferation (turnover) rates such as the skin (epidermis), bone marrow, gastrointestinal mucosa, liver, and testes. Theoretically, the least susceptible organs and tissues are those that replicate very slowly or not at all, including muscle cells, neurons, and cells of the connective tissue (13).

There are important exceptions to the above statement. Neural damage may be caused by commonly used chemotherapeutic drugs, such as methotrexate, vinca alkaloids, and cytosine. Bone injury may be caused by methotrexate, and cardiac sequelae may occur after treatment with doxorubicin (Adriamycin). Importantly, injuries occurring in tissues or organs that have low repair potential because they replicate very slowly or not at all may be of a permanent or long-lasting nature (13). Also important is the finding that risk of late death due to causes other than recurrence is greatest among survivors treated with a combination of chemotherapy and radiotherapy (6).

ISSUES UNIQUE TO CERTAIN CANCER SITES

Late effects have been studied in greater depth for certain cancer sites. The examination of late effects for childhood cancers such as ALL, Hodgkin's disease, and brain tumors have provided the foundation for this area of research. A body of knowledge on late effects of radiation or chemotherapy is subsequently being developed for adult sites, such as breast cancer. For example, studies have evaluated and reported on the development of neurocognitive deficits after chemotherapy for breast cancer, a late effect that was initially observed among survivors of childhood cancer receiving cranial irradiation or chemotherapy. Late effects of bone marrow transplant have been studied for both adult and childhood cancer survivors, as have sequelae associated with particular chemotherapeutic regimens such as Adriamycin, Bleomycin, Vinblastine, Dacarbazine (ABVD) and Mechlorethamine, Oncovin, Procarbazine, and Prednisone (MOPP) for Hodgkin's disease, and Cytoxan, Methotrexate, and Fluorouracil (CMF) and Fluorouracil, Adriamycin, and Cytoxan (FAC) for breast cancer. Chemotherapeutic drugs for which late effects have been reported most frequently include doxorubicin (Adriamycin), bleomycin sulfate, vincristine sulfate, methotrexate, cyclophosphamide, and many others (Table 74-1).

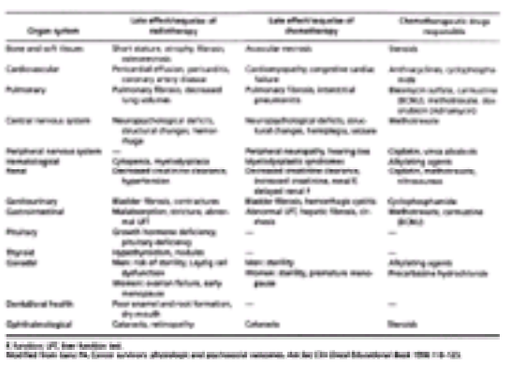

TABLE 74-1. POSSIBLE LATE EFFECTS OF RADIOTHERAPY AND CHEMOTHERAPY

The side effects of radiotherapy, both alone and in conjunction with chemotherapy, have been reported fairly comprehensively for most childhood cancer sites associated with good survival rates. It is important to bear in mind that most cancer treatment regimens consist of chemotherapy in conjunction with surgery or radiation, and multidrug chemotherapeutic regimens are the rule rather than the exception. As such, the risk of late effects must always be considered in light of all other treatment modalities to which the patient has been exposed.

SPECIAL CONSIDERATIONS IN CHILDHOOD CANCERS

Cancer therapy may interfere with development in terms of physical and musculoskeletal growth, neurocognitive/intellectual growth, and pubertal development. These effects may be most notable during the adolescent growth spurt.

Alterations in Physical Growth

Linear Growth Effects

Decreased linear growth is a common problem among children treated for cancer. Catch-up growth leading to resumption of normal growth may occur after treatment so that premorbid growth status is resumed. However, in some survivors, such as those with childhood brain tumors or leukemia, short stature may be permanent or progressive. Whole brain radiation, especially in high doses administered to children younger than 5 years of age, is the principal cause of short stature. This results from injury to the hypothalamo-pituitary axis, which leads to severe growth hormone deficiency. Dosages of 24 Gy may lead to normal baseline levels of growth hormone but an abnormal response to stimulation (14) or atypical patterns of release, especially around the time of puberty (14). If doses of radiotherapy are low, growth velocity may proceed normally until puberty, but the pubertal growth spurt itself may be minimal.

Early onset of puberty is also common after cranial radiation, especially when radiation is administered at younger ages. This leads to a small window of time for the pubertal growth spurt and consequently a reduced ultimate height (15,16). Chemotherapy, especially in combination with radiotherapy, may contribute to decreased linear growth. Chemotherapy alone may cause temporary growth retardation, with resumption of normal growth velocity once treatment ends.

Higher body mass index and obesity, progressive or stable once treatment ends, also has been reported in survivors of childhood leukemia treated with cranial radiation or chemotherapy (17,18 and 19). Vertebral stature loss, seen in brain tumor patients receiving radiation to the whole spine or to the T10-L5 level in dosages greater than 3500 Gy, is impacted by the overall dose and age at radiation (20). These patients may have a reduced sitting (crown to rump) height even in the presence of overall normal height. Treatment of other cancers, such as Wilms' tumor, Hodgkin's disease, medulloblastoma, and sarcoma, may also diminish vertebral growth.

Hypoplasia

Localized radiotherapy can exert a direct, negative effect on musculoskeletal or integumentary growth, leading to a form of growth impairment known as hypoplasia. This occurs especially among children treated with radiation. It usually results from asymmetric radiation fields that may lead to differential growth of the radiated versus nonirradiated tissue. Functional effects reported include radiationinduced scoliosis, which in turn can cause back or muscle pain. Hypoplasia is usually not apparent at the end of therapy and manifests itself with growth, especially the pubertal growth spurt.

Another form of hypoplasia may occur in patients whose adipose tissue is particularly sensitive to radiation, leading to asymmetric fat distribution or weight gain. Breast asymmetry, arrested development, or hypoplasia also may occur after unilateral chest radiotherapy with radiation dosages between 10–20 Gy in the prepubertal period (21).

Alterations in Intellectual Development

The impact of therapy on intellectual outcome is one of the most important sequelae of cancer treatment during childhood. The severity is affected by both the dose of therapy and the age of the child at the time of diagnosis and treatment. In children with leukemia, a variety of neuropsychological abnormalities have been associated with regimens for central nervous system prophylaxis that include whole brain irradiation (22). Specific risk factors for such abnormalities include radiation in doses greater than 24 Gy or the onset of treatment during preschool years (23). Children with these risk factors are more than three times more likely to need special education or to be classified as learning disabled. Attention and visual motor skill deficits may lead to difficulties in reading, language, and arithmetic (24). Preschool children who receive cranial radiotherapy or intrathecal chemotherapy often require special educational resources to learn basic skills after 18–24 Gy of cranial radiotherapy. The same dosages may lead to difficulties with mastering complex information such as a new language or high-level mathematics in older children. Cognitive sequelae may become apparent over time as intellectual growth starts to lag behind the expected course.

Significant cognitive deficits are most likely at doses >36 Gy, administration of radiation therapy for brain tumors before 2 years of age, or after intense intrathecal and infusion chemotherapy for the treatment of childhood leukemia (25). Cognitive sequelae are postulated to occur as a result of cellular neuronal changes that have not yet been well delineated.

Altered Pubertal Development

It is important to monitor pubertal development throughout the pubertal time period since it is difficult to evaluate the extent of treatment-induced gonadal damage during childhood, and because initial pubertal developmental manifestations, such as the appearance of pubic hair, may occur in the presence of severe gonadal damage. Sertoli cells are more sensitive to radiation and alkylating agents than Leydig cells (26). Consequently, boys without Leydig cell damage can experience normal masculinization, potency, and libido even in the presence of azoospermia. Ovaries are less sensitive to gonadotoxic agents than the testes, but secondary gonadal insufficiency due to impaired production of luteinizing hormone or follicle stimulating hormone can occur as a result of cranial radiation, especially in high doses. The effects are more profound in female brain tumor patients receiving hypothalamic-pituitary axis radiation in combination with alkylating agents. In these cases, both direct gonadal effects and secondary gonadal insufficiency may be observed.

SPECIAL CONSIDERATIONS IN ADULT CANCERS

Some late effects of chemotherapy may assume special importance depending on the adult patient's age at the time of diagnosis and treatment. Diagnosis and treatment during the young adult or reproductive years may call for a special cognizance of the importance of maintaining reproductive function and the prevention of second cancers. These are also key issues for children whose cancers are diagnosed during childhood.

Cancer patients diagnosed and treated during middle age may need specific attention to sequelae such as premature menopause; issues relating to sexuality and intimacy; pros and cons of using estrogen replacement therapy; prevention of neurocognitive, cardiac, and other sequelae of chemotherapy; and the prevention of coronary artery disease and osteoporosis. It has been reported that sexual dysfunction persists after breast cancer treatment, despite recovery in other domains, and includes vaginal discomfort, hot flashes, and alterations in bioavailable testosterone, luteinizing hormone, and sex hormone binding globulin (27). Menopausal symptoms such as hot flashes, vaginal dryness, and stress incontinence are very common in breast cancer survivors and cannot be managed with standard estrogen replacement therapy (28). The normal life expectancy of survivors of early-stage cancers diagnosed during these years of life underscores the need to address their long-term health and quality-of-life issues.

Although older patients (older than 65 years) bear a disproportionate burden of cancer, advancing age is associated with increased vulnerability to other age-related health problems and concurrent ailments such as diabetes, chronic obstructive pulmonary disease, heart disease, arthritis, and hypertension. Any of these could potentially affect treatment choice, prognosis, and survival. Hence, cancer treatment decisions may need to be made in the context of the older individual's preexisting health problems (comorbidities). Measures that can help evaluate the existence, nature, and severity of comorbidities among older cancer patients in a reliable manner are needed. Currently, there is little information on how comorbid age-related conditions influence treatment decisions, the subsequent course of the disease, the tolerance of compromised older cancer patients to the stress of cancer and its treatment, and the management of concomitant comorbid conditions (29).

Late and Long-Term Effects By Organ System or Tissues Affected

System-Specific Physiological Sequelae

System-specific sequelae include organ damage or failure, and premature aging due to chemotherapy, hormone therapy, radiation, surgery, or any combination modality therapy.

Cardiac Sequelae

Cardiac damage is most pronounced after treatment with the anthracycline drugs doxorubicin and daunorubicin. These drugs are used widely in the treatment of most childhood cancers and adjuvant chemotherapy for breast cancer. An additive effect has also been reported when anthracyclines are used in conjunction with cyclophosphamide and radiation therapy. Cyclophosphamide alone has been associated with the development of congestive cardiomyopathy, especially when administered at the high doses used in transplant regimens. Anthracyclines cause myocardial cell death, leading to a diminished number of myocytes and compensatory hypertrophy of residual myocytes (30). Major clinical manifestations include reduced cardiac function, arrhythmia, and heart failure (2,3).

Cardiac injury that becomes clinically manifest during or shortly after completion of chemotherapy may progress, stabilize, or improve after the first year of treatment. This improvement may either be of a transient nature or last for a considerable time. There is also evidence of a continuum of injury that manifests itself throughout the lives of patients (31). From a risk factor perspective, patients who exhibit reduced cardiac function within 6 months of completing chemotherapy are at increased risk for the development of late cardiac failure (32). However, a significant incidence of late cardiac decompensation manifested by cardiac failure or lethal arrhythmia occurring 10–20 years after the administration of these drugs has also been reported (33).

Congestive cardiomyopathy is directly related to the total dose of the agent administered. Subclinical abnormalities have also been noted at lower doses. Cardiac toxicity may occur at lower doses when mediastinal radiation is combined with the chemotherapeutic drugs mentioned earlier in this section.

Late onset of congestive heart failure has been reported during pregnancy, rapid growth, or after the initiation of vigorous exercise programs in adults previously treated for cancer during childhood or young adulthood. Decompensation results from increased afterload and the impact of the additional stress of such events on marginal cardiac reserves. Initial improvement in cardiac function after completion of therapy appears to result, at least in part, from compensatory changes. Compensation may diminish in the presence of these stressors or myocardial depressants such as alcohol (2,5).

Effects of radiation on the heart may be profound, and include valvular damage, pericardial thickening, and ischemic heart disease. Adult patients have a markedly increased relative risk (RR) of both angina and myocardial infarction (RR = 2.56) years after mediastinal radiation for Hodgkin's disease, and the RR of cardiac death is 3.1 (34). This risk is greatest among patients receiving >30 Gy of mantle irradiation and those treated before 20–21 years of age. Protecting the heart reduces the risk of cardiac death due to causes other than myocardial infarction (2,3,5,35).

Neurocognitive Sequelae

Progressive dementia has been reported in some long-term cancer survivors as a result of whole brain radiation, with or without chemotherapy, and occurs most often in brain tumor patients and patients with small cell lung cancer who have received prophylactic therapy (2,3). Neuropsychological abnormalities have also been reported after central nervous system prophylaxis using whole brain radiation for leukemia in childhood survivors. Cognitive changes in children received initial recognition as treatments for childhood cancer, especially acute lymphoblastic leukemia (ALL), became increasingly effective. These observations have resulted in changes in treatment protocols for childhood ALL (35,36).

Several studies have reported cognitive dysfunction in women treated with adjuvant therapy for breast cancer (37,38). Additionally, although cranial irradiation is the most frequently identified causal factor in both adults and children, current work in adults indicates that cognitive problems may also occur with surgery, chemotherapy, and biological response modifiers (39,40 and 41). These findings need to be validated in prospective studies along with the interaction between treatment with chemotherapeutic agents, menopausal status, and hormonal treatments. Emotional distress also has been related to cognitive changes in studies of patients beginning cancer treatment.

Patients have attributed problems in cognition to fatigue, and others have reported problems with concentration, short-term memory, problem solving, and concerns about “chemobrain” or “mental pause” (42). Comparisons across studies are difficult because different batteries of neuropsychological tests have been used, and patient samples have varied by diagnosis, age, gender, and type of treatment. There also has been inconsistency in the timing of measures in relation to treatment landmarks. Despite these methodological issues, studies have shown impairments in verbal information processing, complex information processing, concentration, and visual memory (43,44,45 and 46).

Gonadal Toxicity

Treatment-related gonadal failure or dysfunction, expressed as amenorrhea or azoospermia, can lead to infertility in both male and female cancer survivors, and may have its onset during therapy (47). Infertility can be transient, especially in men. The testis is more sensitive to cytotoxic therapies than the ovary, but late recovery has been reported, even though the mechanism of this slow repair is unclear. Reversibility is dependent on the dose of gonadal radiation or alkylating agents. Ovarian

function is unlikely to recover long after the immediate treatment period, and long-term amenorrhea is commonly due to loss of ova. Psychological counseling should be provided to facilitate adjustment to this long-term consequence of therapy. Cryopreservation of sperm before treatment is an option for men, but limited means are available to preserve ova or protect against treatment-related ovarian failure for women (5,48,49).

The risk of premature onset of menopause in women treated with chemotherapeutic agents, such as alkylating agents and procarbazine hydrochloride, or abdominal radiation therapy, is age-related. Women older than age 30 at the time of treatment have the greatest risk of treatment-induced amenorrhea and menopause. There is a sharply increased rate when chemotherapy is administered around the age of 40 years. Tamoxifen citrate has not been associated with the development of amenorrhea (50), but cyclophosphamide at doses of 5 g/m^2 is likely to cause amenorrhea in women older than 40; many adolescents continue to menstruate even after cyclophosphamide doses of >20 g/m^2 (51). Although young women may not become amenorrheic after cytotoxic therapy, the risk of early menopause is significant. Female disease-free survivors of cancer diagnosed at ages 1–19, who were menstruating at age 21, had a four times higher risk of early menopause compared to controls (52).

Direct radiotherapy to the ovaries has also been reported to cause infertility among survivors of Hodgkin's disease and Wilms' tumor (when ovaries were in the radiation field). This outcome reflects a direct effect on the ovaries or an effect on the uterine vasculature leading to an impaired ability of the uterine muscle to grow with pregnancy (53). Cranial radiation may also impair fertility because of deficient gonadotropin from the hypothalamic-pituitary axis. Hyperprolactinemia, another potential effect of hypothalamic-pituitary irradiation, also can affect growth, libido, and fertility (54). The risk is dose dependent at 55 Gy or more of radiation.

The testes are much more sensitive to both radiation and chemotherapy, and sterility has occurred frequently after 10 g/m^2 of cyclophosphamide. Being in a prepubertal state at treatment does not offer much protection to the testes vis-à-vis the effects of cyclophosphamide. In fact, 10% of males have been reported to become sterile after one or two cycles of chemotherapy with the MOPP regimen for Hodgkin's disease, and 80–100% become sterile after six cycles (55). Even low doses of radiotherapy can cause azoospermia in males as spermatozoa are much more sensitive to cytotoxic therapies than the testosterone-producing Leydig cells.

Pulmonary

The acute effects of chemotherapy on the lungs may be lethal, subside over time, progress insidiously to a level of clinical pulmonary dysfunction, or be manifested solely by abnormal pulmonary function tests (2,5). Classically, high doses of bleomycin sulfate have been associated with pulmonary toxicity. However, drugs such as alkylating agents, methotrexate, and the nitrosoureas also may lead to pulmonary fibrosis, especially when combined with radiation therapy. Radiation is thus an important contributor to pulmonary sequelae of chemotherapy (56). Alkylating agents can injure the lung parenchyma, cause restrictive lung disease by inhibiting chest wall growth, and lead to thin anteroposterior chest diameters even 7 years after completion of therapy. Bleomycin sulfate may cause pulmonary insufficiency and interstitial pneumonitis (57).

Pulmonary fibrosis can cause late death in the survivorship period. Among children treated for brain tumors with high doses of nitrosourea and radiotherapy, 35% died of pulmonary fibrosis—12% within 3 years and 24% after a symptom-free period of 7–12 years (58). The risk for overt decompensation continues for at least 1 year after cessation of therapy, and can be precipitated by infection or exposure. to intraoperative oxygen. In terms of long-term outcomes, a recent study noted that 22% of Hodgkin's disease patients with normal pulmonary function tests at the end of therapy (three cycles each of MOPP and ABVD or two cycles of each plus 2550 cGy of involved field radiotherapy) developed abnormalities with follow-up of 1–7 years.

The long-term outcome of pulmonary toxicity is determined by factors such as the severity of the acute injury, the degree of tissue repair, and the level of compensation possible. Pulmonary dysfunction is usually subclinical and may be manifested by subconscious avoidance of exercise owing to symptoms. Premature respiratory insufficiency, especially with exertion, may also become evident with aging. Recent aggressive lung cancer treatment regimens consisting of surgery, radiation, and chemotherapy may well put patients at high risk for decreased pulmonary function and respiratory symptoms.

Genitourinary Tract

Several drugs, such as cisplatin, methotrexate, and the nitrosoureas, have been associated with both acute and chronic toxicities to the genitourinary tract, including glomerular and tubular injury (59). Glomerular injury may recover over time, whereas tubular injury generally persists. Hemodialysis to counteract the effects of chronic renal toxicity may be warranted for some patients. Ifosfamide may cause Fanconi's syndrome, with glycosuria, phosphaturia, and aminoaciduria, and also may affect glomerular filtration. Hypophosphatemia may result in slow growth with possible bone deformity if untreated. Radiation therapy may cause tubular damage and hypertension due to renal artery stenosis, especially when doses are greater than 20 Gy or treatment is given to children (60). Radiation and chemotherapy may act synergistically, the dysfunction occurring with only 10–15 Gy.

The bladder is particularly susceptible to certain cytotoxic agents. Acrolein, a metabolic by-product of cyclophosphamide and ifosfamide, may cause hemorrhagic cystitis, fibrosis, and occasionally, diminished bladder volume. An increased risk of developing bladder cancer also exists. Radiation may lead to bladder fibrosis, diminished capacity, and decreased contractility, with severity proportional to dose and area irradiated. The resultant scarring may diminish urethral and ureteric function (2,5).

Thyroid Gland

Patients receiving radiation therapy to the head and neck may develop subclinical or clinical hypothyroidism. This risk is significant in patients receiving mantle radiation therapy for Hodgkin's disease (61). Compensatory hypothyroidism is manifested initially by elevated thyroid stimulating hormone (TSH) but normal T_3 and T_4 and a clinically euthyroid state. Deterioration of thyroid function leads to clinical symptomatology. Animal studies show that chronically elevated TSH levels in the presence of irradiated thyroid tissue can enhance tumor development. Thyroid disorders observed after thyroid irradiation also include benign nodules (3.3%), Graves' disease (3.1%), thyroid cancer (1.7%), and Hashimoto's thyroiditis (0.7%) (2,5).

Gastrointestinal/Hepatic

There are few studies describing long-term effects to the gastrointestinal system, either due to underdetection or a longer latency period than for other organs. Fibrosis and adhesions are known to occur after radiotherapy to the bowel. Hepatic effects may result from the deleterious effects of many chemotherapeutic agents and radiotherapy. Transfusions may increase the risk of viral hepatitis. Hepatitis C has been identified in increasing numbers of survivors, 119 of 2620 tested (2). Of the latter patients, 24 of 56 who agreed to participate in a longitudinal study underwent liver biopsy. Chronic hepatitis was noted in 83%, fibrosis in 67%, and cirrhosis in 13%.

Compromised Immune System

Hematological and immunological impairments can occur after either chemotherapy or radiation, and are usually acute in nature. They are temporally related to the cancer treatment. Occasionally, persistent cytopenias may persist after pelvic radiation or in patients who have received extensive therapy with alkylating agents. Alkylating agents may cause myelodysplastic syndrome or leukemia as a late sequela. Immunological impairment is particularly seen as a long-term problem in Hodgkin's disease, relating to both the underlying disease and the treatments used. Hodgkin's disease patients are also at risk for serious bacterial infections if they have undergone splenectomy (2,5).

Peripheral Nerve

Peripheral neuropathy is common after treatment with paclitaxel, vincristine sulfate, and cisplatin. However, despite the frequent use of such chemotherapeutic agents, few studies have characterized the nature and course of neuropathies associated with these drug regimens or dose levels (62,63). Peripheral neuropathy may or may not resolve over time, and potential residual deficits are possible. Clinical manifestations may include pain, paresthesias or sensory loss, or weakness and clumsiness in the hands and feet years after completion of cancer treatment.

SECOND MALIGNANT NEOPLASMS AND RECURRENCE

After cancer therapy, there may be an increased risk of second primary cancers or recurrence of the primary disease. This risk may be related to the neoplasm itself or the antineoplastic therapy. Examples include the development of breast cancer after Hodgkin's disease, ovarian cancer after primary breast cancer, and cancers associated with the HNPCC gene.

Survivors of childhood cancer have an 8–10% risk of developing a second malignant neoplasm within 20 years of the primary diagnosis (64,65). This is attributable to the mutagenic risk of both radiotherapy and chemotherapy. This increased risk may be further potentiated in patients with genetic predispositions to malignancy. The

risk of secondary malignancy induced by cytotoxic agents is related to the cumulative dose of drug or radiotherapy (dose-dependence) (3).

The risk of malignancy with normal aging results from the risk of cumulative cellular mutations. Compounding the normal aging process by exposure to mutagenic cytotoxic therapies results in an increased risk of secondary malignancy, particularly after radiotherapy, alkylating agents, and podophyllotoxins. Commonly cited secondary malignancies include (a) leukemia after alkylating agents and podophyllotoxins (66); (b) solid tumors such as breast, bone, and thyroid cancer in the radiation fields in patients treated with radiotherapy (68); (c) bladder cancer after cyclophosphamide; (d) a higher risk of contralateral breast cancer after primary breast cancer; and (e) ovarian cancer after breast cancer (2,5).

The leukemias tend to arise earlier, 2–3 years after podophyllotoxins and 5–10 years after alkylating agents. In contrast, the latent period for many of the solid tumors is 10–20 years or longer (3). Breast cancer in women treated with conventional dose radiotherapy during the peripubertal period is of particular concern, with studies showing that more than half of these individuals may develop breast cancer by the age of 40 years (67). Older adolescents should be taught breast self-examination, whereas survivors in their twenties may benefit from mammograms, ultrasound, and annual clinical breast examinations. Relevant screening tests for diverse cancer sites should also be considered in other populations at high risk (3).

The genetic risk of a second cancer is very prominent in patients with an abnormal retinoblastoma gene (68). Children with hereditary retinoblastoma may have a 60% risk of secondary malignancy by the age of 30–40 years (69). The lag time between the first and second malignancy is shortened in this group with exposure to radiotherapy. Patients with the Li-Fraumeni syndrome, characterized by the presence of an abnormal p53 gene, are also at increased risk for second malignant neoplasms. The p53 gene limits a cell's ability to stop proliferating after chromosomal damage has occurred. Women with BRCA I and II are at a higher risk of a second primary in the breast, and ovarian cancer. Finally, the HNPCC families are at high risk of developing several associated cancers (2,3,5).

Ancillary Sequelae

Lymphedema

Lymphedema can occur as a persistent or late effect of surgery or radiation treatment. It has been reported most commonly after breast cancer treatment, which yields incidence rates ranging between 6% and 30% (70). Lymphedema can occur in anyone with lymph node damage or obstruction to lymphatic drainage. Women undergoing axillary lymph node dissection and high-dose radiotherapy to the axilla for breast cancer are regarded as the highest risk group. Clinically, lymphedema symptoms may range from a feeling of fullness or heaviness in the affected limb to massive swelling and major functional impairment. Recommendations from the American Cancer Society's conference on lymphedema in 1998 emphasize the need for additional research on prevention, monitoring, early intervention, and long-term treatment. Treatments suggested encompass multiple modalities, including skin care, massage, bandaging for compression, and exercise. Intermittent compression pumps were recommended only when used as an adjunct to manual approaches within a multidisciplinary treatment program, and routine use of medications such as diuretics, prophylactic antibiotics, bioflavinoids, and benzopyrones was discouraged in the absence of additional research. The impact of sentinel node biopsy in lieu of extensive axillary node dissection procedures for breast cancer on the incidence of lymphedema is not known at this time.

Fatigue

Fatigue has been reported as a persistent side effect of treatment in many studies (71,72,73 and 74). This is especially true among patients who have undergone bone marrow transplant (75). Treatment-related fatigue may be associated with various factors, such as anemia, infection, changes in hormonal levels, lack of physical activity, cytokine release, and sleep disorders (76). The impact of exercise interventions on fatigue is a promising area of research. Fatigue is an important influence on quality of life for both the patient and the family and needs to be managed effectively.

Sexuality and Intimacy

Sexuality encompasses a spectrum of issues ranging from how one feels about one's body to the actual ability to function as a sexual being, and has been reported as a persistent effect of treatment. In a recent study on breast, colon, lung, and prostate cancer survivors, issues related to sexual functioning were among the most persistent and severe problems reported (77,78). Preexisting sexual dysfunction may also be exacerbated by cancer and its treatment.

Other Issues

There are numerous functional and cosmetic changes, and comorbidities, that may occur as late effects. These are addressed in other chapters of this volume.

FOLLOW-UP CARE FOR LATE AND LONG-TERM EFFECTS

Optimal follow-up of survivors includes both ongoing monitoring and assessment of persistent and late effects of cancer treatment, and the successful introduction of appropriate interventions to ameliorate these sequelae. This is challenging, and must recognize both the importance of preventing premature mortality from the disease or its treatment, and the prevention or early detection of the physiological and psychological sources of morbidity. The prevention of late effects, second cancers, and recurrences of the primary disease requires watchful follow-up and optimal use of early detection screening techniques. Physical symptom management is as important in survivorship as it is during treatment. Effective symptom management during treatment may prevent or lessen lasting effects.

There has been no consensus on overall recommendations for routine follow-up after cancer therapy. Regular monitoring of health status post–cancer treatment is recommended because it should (a) permit the timely diagnosis and treatment of long-term complications of cancer treatment; (b) provide the opportunity to institute preventive strategies such as diet modification, tobacco cessation, and other lifestyle changes; (c) facilitate screening for, and early detection of, a second cancer; (d) allow timely diagnosis and treatment of recurrent cancer; and (e) improve the detection of functional, physical, or psychological disability.

Follow-up care and monitoring for late effects is usually done more systematically and rigorously for survivors of childhood cancer while they continue to be part of the program or clinic. The monitoring of adult cancer patients for the development of late effects, particularly outside oncology practices, is neither thorough nor systematic. It is important that survivors of both adult and childhood cancers be monitored at regular intervals for the late and longterm effects of treatment.

The patient's age at diagnosis, side effects of treatment reported or observed during treatment, calculated cumulative doses of drugs or radiation, and an overview of late effects most likely for a given patient given the treatment history should be summarized and kept on file. A copy of this summary should be provided to the patient, or to the parent of a child who has undergone treatment for cancer. The importance of conveying this detailed treatment history to primary care providers should be clearly communicated, especially if follow-up will occur in the primary/family care setting. Finally, screening tests that may help detect subclinical effects that could become clinically relevant in the future should be listed.

Recommendations for follow-up of certain documented late effects, based on the literature reviewed earlier (Table 74-2), appear in the following sections. The relevance of each recommendation differs by site of disease, extent of treatment, and age at diagnosis.

TABLE 74-2. FOLLOW-UP CARE AND SURVEILLANCE FOR LATE EFFECTS

Women who are contemplating a pregnancy, and those who are pregnant, should be evaluated by a cardiologist. Obstetricians should be made aware that women who have a history of anthracycline treatment for cancer or chest wall radiation may have limited ability to compensate for the increased blood volume and requisite increased cardiac output of pregnancy. Careful monitoring during pregnancy, particularly the postpartum period, is essential. Pregnancy may carry an unacceptable risk for women with significantly limited cardiac reserves in the setting of treatments as described above.

Screening tests, such as dobutamine stress echocardiography, can detect myocardial injury in the majority of anthracycline-treated patients, even at cumulative doses of 45 mg/m^2 (79). If myocardial injury has occurred, clinical response to diuretics and digoxin is only temporary, and the patients may ultimately die of cardiac causes. Improvement in cardiac function can be significant with afterload reduction. It remains to be determined whether such an intervention can delay or even prevent late decompensation in patients at risk.

Neurocognitive Sequelae

Patients reporting severe persistent cognitive problems or those who are extremely concerned about cognitive changes may be referred to a neuropsychologist for a specific diagnosis and compensatory or remediation techniques. Cognitive problems of recent onset and a history of worsening over time should be evaluated. Written appointment cards, appointment reminder calls or letters, simple printed information about medications, and printed instructions about laboratory work or tests that need to be done before a follow-up appointment are examples of provider-initiated actions that can be helpful to patients experiencing deficits in short-term memory.

Gonadal Toxicity

Early hormone replacement therapy should be considered in women who develop premature menopause, unless contraindicated, to reduce the risk of accelerated osteoporosis and premature heart disease related to estrogen deficiency. Prediction of fertility in an adult female survivor can usually be determined by evaluation of the menstrual cycle and age at treatment because the same dose of chemotherapeutic drug or radiation is more likely to affect an older person than a younger one. Emerging reproductive technologies, artificial insemination, and sperm banking are being shown to be beneficial in terms of pregnancy outcomes for infertile or sterile survivors. Appropriate endocrinological interventions with bromocriptine mesylate and similar dopamine agonists may be helpful. For boys receiving higher doses of therapy, testosterone levels as well as pubertal development should be assessed. During early adolescence, testosterone levels in the lower ranges of normal for an adult male are to be expected. By late puberty, testosterone deficiency should be treated in order to normalize libido and masculinization (78). Female cancer survivors experiencing pubertal delay and amenorrhea may need hormone therapy to initiate and maintain feminization, and to prevent osteoporosis and early coronary artery disease.

Pulmonary Sequelae

Patients treated with pulmonary radiation and cytotoxic agents such as carmustine (BCNU), lomustine (CCNU), and bleomycin sulfate should undergo pulmonary function tests every 5–8 years. This is important because symptomatic decompensation of pulmonary function may occur even a decade after treatment with nitrosourea or other agents. Patients who have been exposed to these therapies should be counseled to avoid exposure to pulmonary toxins and cigarettes.

Urinary Tract

The kidney and bladder are the most susceptible sites vis-à-vis late effects. Patients who have received cyclophosphamide or ifosfamide should have an annual urinalysis. Detailed urological workup should occur if hematuria is reported.

Thyroid Gland

Annual assessment of TSH should be performed in patients with a history of mantle radiation therapy for Hodgkin's disease. Treatment with thyroid hormone may be instituted if there is persistent evidence of compensated hypothyroidism.

Peripheral Neuropathy

Patients at high risk or those who report persistent neuropathy should be identified and monitored. Changes in sensation in the hands and feet, paresthesias, constipation, bladder problems, vision, hearing, muscle strength, sexual dysfunction, and changes in gait should be assessed, and physical examination performed, at each visit. The location and extent of neuropathy should be documented. A referral to a specialist for consultation and examination may be beneficial. Routine inspection of the feet for injuries, special care in fitting shoes, avoiding high-risk situations like walking barefoot, and using care in toenail trimming are logical self-care recommendations for sensory manifestations. For peripheral neuropathy manifested as pain or burning, referral to a pain management specialist is appropriate.

Lymphedema

Patients should be asked about the presence or development of swelling, or sensations of aching or fullness, in areas distal to treated lymph nodes or the arm on side of the axillary dissection. General cautions to avoid injuries to the skin on the affected limb, including venipunctures, and cleaning cuts and scratches when they occur, should be observed.

Fatigue

Specific causes of fatigue such as decreased thyroid function, persistent anemia, infection, compromised pulmonary function, sleep problems, cardiac problems, and physical deconditioning should be investigated. Underlying physiological problems should be treated. Physical activity such as regular walking may be helpful.

Surgical Toxicity

Pneumococcal vaccine before splenectomy and then every 5–7 years is recommended. A penicillin or alternative antibiotic should be used for prophylaxis or illness. Medical care should be sought (and antibiotic coverage administered) at the first sign of fever.

Screening

There are no evidence-based guidelines for cancer screening or surveillance in individuals with a past history of cancer. It is logical that cancer survivors follow general guidelines for cancer screening recommended for adult men and women, such as regular examination of the skin, colorectal cancer screening with either stool occult blood testing or sigmoidoscopy, regular Pap smear, and annual mammograms after age 40 (age 30 for female survivors of Hodgkin's disease treated with mantle radiation), depending on the site of primary cancer. It may also be a good idea to screen for associated cancers in patients who were diagnosed at ages younger than commonly reported for a given cancer, those with a positive family history of cancer, or those with a rare hereditary susceptibility gene such as BRCA I and II or HNPCC.

For the prevention of second malignant neoplasms occurring as a late effect of treatment, such as breast cancer after Hodgkin's disease, hematological malignancies, bladder cancer, and sarcomas within a radiation port, a detailed history and physical examination, complete blood counts, routine urinalysis, and screening modalities such as those already mentioned should be part of the follow-up plan.

Physicians, caregivers, and the family must be able to hear and observe what the patient is trying to communicate, reduce fear and anxiety, counter feelings of isolation, correct misconceptions, and obtain appropriate symptom relief. Practitioners inheriting care for child or adult survivors need to understand the effects of cytotoxic therapies on the growing child or the adult at varying stages/ages of life, and be knowledgeable about interventions that might mitigate the effects of these treatments.

Patient education should guide lifestyle and choices for follow-up care, promote adaptation to the disease or relevant sequelae, and help the patient reach an optimal level of wellness and functioning, both physical and psychological, within the context of the disease and treatment effects.

GRADING OF LATE EFFECTS

Grading of late effects can provide valuable information for systematically monitoring the development or progression of late effects. There is, to date, no universally accepted grading system. Garre et al. developed a set of criteria to grade late effects by degree of toxicity as follows: grade 0 (no late effect); grade 1 (asymptomatic changes not requiring any corrective measures, and not influencing general physical activity); grade 2 (moderate symptomatic changes interfering with activity); grade 3 (severe symptomatic changes that require major corrective measures and strict and prolonged surveillance); and grade 4 (life-threatening sequelae) (80). The Swiss Pediatric Oncology Group grading system has not been validated so far (81). It also ranges from 0–4, as follows: grade 0 (no late effect); grade 1 (asymptomatic patient requiring no therapy); grade 2 (asymptomatic patient, requires continuous therapy, continuous medical follow-up, or symptomatic late effects resulting in reduced school, job, or psychosocial adjustment while remaining fully independent); grade 3 (physical or mental sequelae not likely to be improved by therapy but able to work partially); and grade 4 (severely handicapped, unable to work independently). It is important to be aware that these tools are available, to validate them in larger populations, and to examine their usefulness in survivors of adult cancers.

CONCLUSIONS

A large and growing community of cancer survivors is one of the major achievements of cancer research over the past three decades. Both length and quality of survival are important end points. Many cancer survivors are at risk for, and develop, physiological late effects of cancer treatment that may lead to premature mortality and morbidity. As in the past, when treatments were modified to decrease the chance of developing toxicities among survivors of childhood cancer, the goal of future research and treatment should also be to evaluate late effects systematically and further modify toxicities without diminishing cures. Interventions and treatments that can ameliorate or effectively manage both persistent and late physical effects of treatment should be developed and promoted for use in this population. Oncologists, primary care physicians, and ancillary providers should be educated and trained to effectively monitor, evaluate, and optimize the health and wellbeing of a patient who has been treated for cancer.

Additional research is needed to provide adequate knowledge about symptoms that persist after cancer treatment or those that arise as late effects. Prospective studies that collect data on late effects are needed, as most of the literature on late effects is derived from cross-sectional studies. It may not be clear from these studies whether a symptom began during treatment or immediately posttreatment. Continued, systematic follow-up of survivors will result in information about the full spectrum of damage caused by cytotoxic or radiation therapy, and possible interventions that may mitigate the effects. Interventions, therapeutic or lifestyle, that can ameliorate these late effects need to be developed. Practice guidelines for follow-up care of cancer survivors and evaluation and management of late effects must be developed so that effects can be mitigated when possible.

Our knowledge about the late effects of cancer treatment, in large part, comes from studies conducted among survivors of pediatric cancer. We need to explore further the impact of cancer treatment on late effects in survivors diagnosed as adults. We also need to examine the role of comorbidities on the risk for, and development of, late effects of cancer treatment among these adult cancer survivors.

Each person with cancer has unique needs based on the extent of the disease, effects of treatment, prior health, functional level, coping skills, support systems, and many other influences. This complexity requires an interdisciplinary approach by health professionals that is organized, systematic, and geared towards the provision of high-quality care. This may facilitate the adaptation of cancer survivors to temporary or permanent sequelae of the disease and its treatment.

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PSYCHOSOCIAL ASPECTS OF CANCER SURVIVORSHIP

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> What happens when my body breaks down happens not just to that body but also to my life, which is lived in that body. When the body breaks down, so does the life. Even when medicine can fix the body, that doesn't always put the life back together again (1).
>
> —Arthur Frank

Survivorship is not just about long-term survival but about quality of life from the moment of diagnosis onward. To better understand this issue from the consumer's perspective, it is helpful to understand the difference between curing and healing. The concept of cure has become a medical reality for many types of cancer; yet, the concept of healing after cancer and its treatment is a completely different story. Although curing resides within a disease-repair system and is defined biomedically, healing focuses on health and wellness and can be explained both physically and psychosocially. *Disease* is what is seen, treated, and measured and is the tangible focus for cure. *Illness* is what is felt and experienced and is a more intangible focus for healing. Lerner notes that, “Although the capacity to heal physically is necessary to any successful cure, healing can also take place on deeper levels whether or not physical recovery occurs” (2). By understanding the difference between the treatment of an external disease and the personal, lived experience of illness, physicians can more readily acknowledge and appreciate the psychosocial sequelae, which may include spiritual or existential influences, that often accompany or follow a diagnosis of cancer. This chapter will attempt to redefine the cancer experience, especially from the consumer's perspective, review psychosocial aspects of survival along an expanded continuum, and offer strategies to enhance survivorship.

CANCER MYTHS

At the beginning of fall semester, 1995, the question, “What does cancer mean to you?” was posed to a class of second-year medical students at the University of Arizona. Their responses reflect current feelings within Western society as a whole and include descriptives such as *death, terminal, sadness, fear, chemotherapy, mutilation, pain, financial loss*, and, last but not least, *cure*. Their attitudes about cancer echo the generally negative sentiments that would have been expected decades ago. The only positive word was *cure*, and it was at the bottom of the list.

Cancer continues to instill dread and to masquerade as a ruthless, secretive assailant. Early in this century, it was believed that, “If it was not fatal, it was not cancer” (3). In *Illness as Metaphor*, Sontag (3) writes that a diagnosis of cancer will remain an automatic death sentence until its causes are known and effective treatments are discovered. Even though recent advances in science and medical technology have increased the chances for survival, the often paralyzing fear of eventual death from the disease still lingers today. This fear will obviously continue to invade our lives as long as certain types of cancer are untreatable or incurable.

Along with the myth of imminent death, cancer evokes other misunderstandings, especially concerning causation. Decades ago, many people theorized that cancer was caused by emotional resignation and hopelessness (3). Although attempts to identify “cancer personalities” became a popular trend in the 1970s, there were suggestions that patients unfortunate enough to be diagnosed with cancer must have done, thought, or repressed something to allow this disease to happen. Current pop psychology that often oversimplifies causation and blames the sick individual for having done something wrong may be rooted in this myth. Although the paranoia surrounding cancer is gradually diminishing, the disease continues to harbor elements of fear, stigma, shunning, discrimination, and withdrawal of support (4).

When the biology of a disease is not understood, mythological speculation and oversimplification are apt to define the sickness. Of major importance in defining cancer is that it continues to be identified as a homogeneous disease. Cancer is less often seen as many diseases with multiple causes and treatments and more frequently seen as a single entity with simple causation. The prevalent idea that stress causes cancer often overrules other causative factors, such as genetic predisposition, decreased or damaged immune competence, dangerous health habits, and environmental carcinogens. But not all myths are rooted in the individual. The health care system itself is also full of myths and misunderstandings.

HEALTH CARE MYTHS

As medical researchers and clinicians focus on extending and saving lives, patients become acutely aware of issues affecting the quality of their lives. Two current myths involved with quality of life concerns are (a) the allpowerful role of the physician, and (b) the healing environment within our hospitals (4).

The power and control in the management of patients was historically held by doctors. In this current age of increased bureaucracy, expensive delivery of care, and cost containment, decision-making powers are now shifting to financing and regulatory agencies (5). Physicians are required to spend increasing amounts of time on administrative matters, which decreases the amount of time available for patient care. Patients have longer waits for appointments, and the choice of doctors is more limited. Meanwhile, out of necessity a new prototype of health care consumer is emerging. Consumers who are more assertive in asking questions and requesting information are more inclined toward partnership *with* rather than paternalism *from* their providers of care. As the decision-making powers shift, this attitude can either enhance or strain the already challenged physician-patient relationship.

The second area of misunderstanding is the type of environment in which healing is fostered. The delivery of care is now complicated by diagnosis-related groups, gatekeepers, cost containment, utilization reviews, managed care, and mountains of paperwork. While the old system allowed unlimited stays in the hospital and actually encouraged passivity and invalidism, the new system has gone to the other extreme. Because discharging patients from the hospital as soon as possible has become fiscally prudent, patients return home sooner and sicker. The healing environment, then, becomes the home rather than the hospital, and greater responsibility is placed on the patient and family members or other caregivers. These changing social trends are actually forcing a shift from passive patienthood to a more proactive survivorship.

SEMANTICS OF SURVIVORSHIP

The concept of survivorship was initially introduced to the field of oncology in 1986 with the founding of the National Coalition for Cancer Survivorship. The events preceding this organizational meeting included medical advances and social trends that provoked exploration of new issues related to cancer. As new therapies became available to treat cancer, the hopes and expectations of surviving this disease were elevated. Access to information about scientific breakthroughs became readily available to the general public; awareness about cancer prevention, early detection, second opinions, and treatment options increased; many types of cancers shifted from acute to chronic diseases; and some patients were actually cured. Oncologists were finally able to rejoice, along with their patients, because not everyone

would die of this feared disease. Yet, as patients and family members savored the sweetness of survival, they also realized that life would never be the same and that it would always be full of uncertainty. In *Of Dragons and Garden Peas*, wherein a patient talks to doctors, Trillin sums up this dilemma: “So, once we have recognized the limitations of the magic of doctors and medicine, where are we? We have to turn to our own magic, to our ability to 'control' our bodies” (6).

Control comes in many forms. Before this decade, the cancer patient's agenda was more often than not set by health care providers, especially physicians. Eventually, patients decided to take more control, either directly or indirectly, over all aspects of cancer care that affected their lives. Thus, support groups, hotlines, resource materials, and patient networks proliferated. As the shift to recognize the consumer voice began, the concept of *survivorship* emerged.

Mullan describes survivorship as “the act of living on . . . a dynamic concept with no artificial boundaries” (7). Carter further describes this theme as a process of *going through*, suggesting movement through phases (8). From these models, the concept of survivorship is viewed as a continual, ongoing process rather than a specific time frame, stage, or outcome of survival (9). Survivorship is not just about long-term survival, which is how the medical profession generally defines it. Rather, it is the experience of living with, through, or beyond cancer (10,11). From this point of view, survivorship begins at the moment of diagnosis and continues for the remainder of life (7).

Other discrepancies in semantics revolve around who is or is not a cancer survivor. When cancer was considered incurable, the term *survivor* applied to the family members whose loved one had died of the disease. This terminology was used for years by the medical profession and insurance companies. But when potentially curative therapy became a reality, physicians selected a 5-year parameter to measure survival. Freedom from disease and biomedical longevity became the standards of success where the outcome was measurable and quantifiable.

As treatment successes improved over the years, this limited definition failed to consider patients who are not cured of their disease, require maintenance therapy, or periodically change treatment modalities, yet remain alive for more than 5 years. Others experience late recurrences, are diagnosed with second malignancies, or develop delayed effects of treatment. Even as the 5-year landmark has been modified as a parameter for describing survival, medical professionals seem inclined to categorize anyone receiving therapy or not completely free of disease as a “patient” and everyone who is not under treatment or with no evidence of disease as a “survivor.”

Many people who have histories of cancer feel that survivorship extends far beyond the restrictions of time and treatment. As the empowered consumer encourages the shift from paternalism to partnership, survivors began describing themselves as victors, graduates, triumphers, veterans, and thrivers. Later came a greater sense of power as survivors became activists, advocates, and warriors. More recently, an African-American group considered survivorship a spiritual journey and asked to be called “the blessed.” While all these labels can confuse providers and consumers alike, Gray (12) notes in *Persons With Cancer Speak Out* that, “The act of defining is an act of power.” This is all about the people—the survivors—identifying their own issues and defining themselves rather than relying on the agendas and descriptives of the health care community (9). Any or all of these labels can be considered correct, both quantitatively and qualitatively; they simply need to be defined within the context in which they are used. Thus, the term *survivor* in this chapter reflects the National Coalition for Cancer Survivorship definition: “from the time of its discovery and for the balance of life, an individual diagnosed with cancer is a survivor” (7).

STAGES OF SURVIVAL

Obviously, cancer survivors have different issues, depending on their circumstances along the survival continuum. In the classic article, “Seasons of Survival: Reflections of a Physician with Cancer,” Mullan (13) was the first to propose a model of survival that includes acute, extended, and permanent stages.

Acute Stage

The acute (or immediate) stage begins at the time of the diagnostic workup and continues through the initial courses of medical treatment. The survivor is commonly called a *patient* during this stage, and the primary focus is on treating the disease and physical survival. Usually, without any prior training, persons diagnosed with cancer are required to make sophisticated medical decisions at a time of intense vulnerability, fear, and pressure. Inexperienced in navigating the complicated culture of medicine, many survivors continue to rely solely on their physicians to make treatment-related decisions. Others, though, ask for information, explanations, and more effective communication in an attempt to understand their choices.

Although supportive care services are most available at this time in many oncology arenas, their availability is at risk due to current cost constraints. Yet, access to the health care team, counselors, patient support networks, resource libraries, hotlines, advocacy organizations, and family support systems helps survivors navigate this stage. But the picture changes, sometimes dramatically, once treatment ends.

Extended Stage

If the disease responds during the initial course of therapy, the survivor moves into the extended (or intermediate) stage of survival. This stage is often described as one of watchful waiting, limbo, or remission, as survivors monitor their bodies for symptoms of disease recurrence. Uncertainty about the future prevails, as medical-based support systems are no longer readily available. Recovery entails dealing with the physical and emotional effects of treatment, and reentry into social roles is often challenged by ignorance and discrimination.

Although no longer a patient, the person may not feel entirely healthy and may have difficulty feeling like a survivor. Ambiguity defines this stage, as survivors find themselves afloat in a mixture of joy and fear, happy to be alive and finished with treatments, yet afraid of what the future may hold.

The need for continued supportive care during this transitional stage has recently received attention (7,8,9,10 and 11). Community and peer networks often replace institutional support, and recovery entails regaining both physical and psychological stamina.

Permanent Stage

A certain level of trust and comfort gradually returns, and survivors enter the permanent (or long-term) stage of survival. This is roughly equivalent to cure or sustained remission. Although most survivors experience a gradual evolution from a state of “surviving to thriving,” as described by Hassey-Dow (14), others must deal with the chronic, debilitating, or delayed effects of therapy. Although many of these long-term survivors have no physical evidence of disease and appear to have fully recovered, the life-threatening experience of having survived cancer is never forgotten. The metaphor of the Damocles syndrome illustrates the apprehension or fear of living under the sword, never knowing whether or when it might drop (15,16).

For many cancer survivors, long-term follow-up tends to be as unpredictable as today's health care system. Generally, there are scant, if any, guidelines for specific follow-up, nor are there wellness-focused programs tailored to the altered health care needs of this population. One exception is pediatric oncology, which is far beyond adult oncology in the systematic follow-up of long-term survivors. Standardized assessments in specialized clinics help identify problems, such as disease recurrence, second malignancies, or late effects of treatment, and interventions can be initiated as soon as possible.

Adults, on the other hand, often feel burdened by a “glorification of recovery” (17), whereby they are praised for overcoming adversity and encouraged to minimize their complaints. The appearance of health can actually hamper the identification of real problems, as no one wants to believe that something might still be wrong (17,18). But symptoms of distress, both biomedical and psychosocial, must be taken seriously. And, in this age of cost containment and managed care, survivors need continued access to appropriate specialists who understand the consequences of survival and can treat accordingly.

As the population of cancer survivors increases, attention to survival issues needs to be encouraged. Even if the disease is eradicated, the psychosocial sequelae of surviving a life-threatening experience must be recognized as barriers to a full recovery.

PSYCHOSOCIAL ASPECTS

How well an individual adapts psychologically and socially to living with cancer depends on a wide variety of factors. First are the physical factors, including the age and sex of the individual, the type and stage of disease, the kinds and duration of recommended treatments, the outcomes of treatment, disease progression, and residual side effects. Added to these are permanent disabilities, physical limitations, and possible disfigurement and altered body image. Next are the psychological variables. Where is the individual in life-stage development? What previous experiences has the person had with illness in general and with cancer in particular? What individual psychological strengths and weaknesses are brought to the cancer experience? What kinds of coping mechanisms usually are employed by the individual in crisis situations? Does the individual have a history of emotional problems such as depression, anxiety, or other mental health concerns? Self-esteem, independence and motivation, as well as interactional skills, also play a part.

When aspects of social functioning are added to the equation, many other variables need to be considered. These include the sociodemographic factors such as marital status, race, ethnicity, religious orientation, educational level, employment history, and financial stability. Next are the social roles ascribed to the individual such as spouse, parent, employee, and friend. In addition to the sociodemographic variables, other social factors include the type of social support available to the individual. What kinds of changes will a history of cancer bring for the individual and the family? Will the individual be able to fulfill existing job requirements, or will joblessness or employment discrimination become a factor? Despite this wide range of individual variability, there are numerous shared experiences that occur along the continuum of cancer survivorship. Also shared are the most common problems and needs faced by persons with cancer.

Needs of Cancer Survivors

Houts and his colleagues (19) conducted one of the most comprehensive studies to date on the needs of cancer survivors. They interviewed a random sample of 629 persons who had been diagnosed with cancer within the past 2 years and also interviewed 397 persons involved in their care. Four major categories of unmet needs were identified: (a) emotional/social needs (including family issues), (b) economic needs (financial, insurance, and employment issues), (c) medical staff needs (the need for information and increased availability), and (d) community needs (including home care and transportation) (19).

In 1988, the Canadian Cancer Society conducted a needs assessment with over 2000 persons who had been diagnosed with cancer or had had a cancer recurrence between 1982 and 1989 (20). Subjects were selected to represent a cross section of types and stages of cancer and various geographical locations. The greatest needs identified were for prompt medical attention, emotional support, pain management, practical assistance, attention to employment and financial problems, and information.

Loescher and her colleagues (21) evaluated the needs of long-term survivors of adult cancer using the Cancer Survivor Questionnaire. They interviewed a small sample of individuals more than 2 years after cancer therapy. Deduction content analysis revealed several themes. The needs identified were for reassurance, control, information, insurance coverage, and money as well as the need to talk about the cancer experience.

In one of the most recent quality-of-life studies in longterm cancer survivors, Ferrell and colleagues (22) used a mailed survey approach to assess the quality of life of 687 cancer survivors. Of the four domains of well-being (physical, social, psychological, and spiritual) that were evaluated using a Quality of Life–Cancer Survivors Tool, the psychological wellbeing subscale had the lowest score. The authors conclude that while distress related to the cancer experience abates over time, the psychological impact of the distress lingers.

Addressing the wide variety of psychosocial needs and concerns of cancer patients mentioned above is beyond the scope of this chapter. However, several salient themes have been selected to receive expanded coverage and to indicate some psychosocial sequelae that perhaps are specific to the cancer experience.

Normlessness (Lack of Societal Norms) of the Cancer Experience

Many of the psychological problems associated with cancer are related to a lack of knowledge and requisite skills needed for negotiating the cancer experience. Cancer survivors experience a sequence of crises for which habitual problem-solving activities are not adequate and that do not lead to the previously achieved balanced state (23). Therefore, cancer may be a normless or anomic situation for a significant number of persons.

Anomia can be defined as “a temporary state of mind occasioned by a sudden alteration in one's life situation, and characterized by confusion and anxiety, uncertainty, loss of purpose, and a sense of separateness from one's usual social support system” (24). Persons newly diagnosed with cancer may not know how to think or talk about their situation. They need information, but because of the shock and unfamiliarity of the situation, they may be unable to understand the broad significance or assimilate what information they do receive.

Added to this is the stigma that accompanies a cancer diagnosis. Despite treatment advances and extended survival rates for various cancers, cancer remains a stigmatized disease, and persons with cancer must contend with the consequent societal attitudes, prejudices, and discrimination (1,3).

Eventually, most persons with cancer become expert about their own illness and treatment. They know more or less what to expect medically, and they learn how best to navigate the health care system. They develop the requisite language and needed coping skills to manage the crisis periods. They often interact with other cancer patients, and perhaps by attending support groups or with the help of their medical team and counselors, they find that while the disease of cancer is a personal experience, there are numerous commonalities among individuals regarding the illness process and its consequences. In short, they learn how to live with cancer. There may be recurrent crisis situations, both physical and psychosocial, but gradually the normlessness first experienced after the cancer diagnosis subsides, and life takes on a somewhat normal, albeit a “new normal,” cadence that incorporates the physical, emotional, and spiritual changes catalyzed by the cancer experience (25).

Problems with Reentry

For many patients, active cancer therapy eventually ends, but the successful end of cancer treatment does not necessarily signal an end to the difficulties and stresses faced by persons with cancer and their family members. The period of waiting to see whether the treatment abated the disease process, and worry about not receiving any active intervention, may create new anxiety and fear (26). The survivor enters what Hurt and her colleagues (27) refer to as “neutral time”: a period of remission characterized by uncertainty and lacking in “safety signals” indicating that the disease will not return. At this time, some individuals face an illness-related identity crisis. They may no longer be perceived as cancer “patients” because they are not in active treatment, yet they may have difficulty thinking about themselves as cancer “survivors” or achieving reentry into a “well-role” (11). Another anomic situation, what Maher (24) refers to as “the anomia of good fortune,” may occur.

When the concept of anomia is applied to cancer recovery, the positive experience of doing well, perhaps even of being cured, may be mixed with negative elements. These elements might include: (a) the withdrawal of the intensified social support that accompanied diagnosis and treatment, (b) ambivalence about the discontinuation of treatment, (c) anxiety about recurrence of disease, (d) adjustment to permanent disabilities resulting from the disease or its treatment, (e) the need to resume life-oriented modes of thought after a successful adjustment to the idea of death, (f) anger at perceived inadequacies, or (g) confusion about feelings of depression when the objective situation has improved (24).

Reentry also entails problems with assuming previous roles and responsibilities, and with readjustment and readaptation to daily life (28). The stress of a diagnosis of cancer and its subsequent treatment disrupts the patterns of a lifetime and requires adaptation to personal and interpersonal changes. While active treatment is ongoing, family members frequently assume some of the instrumental, and even emotional, duties of the person with cancer. This redistribution of tasks can have a marked impact on the family unit. When cancer treatment ends, interpersonal relationships may be further strained because the new patterns of interaction and functionality need to be negotiated once again. Another area of reentry that may be of concern for some cancer survivors is rejoining the workforce. The majority of persons with cancer remain actively employed during the treatment phase, but some experience brief or extended absences from work. Returning to work can entail various psychological stresses. There may be a difference in the way the employee is treated by others. Some co-workers may still believe that cancer carries an automatic death sentence and may stigmatize and isolate the returning employee. There may be changes in physical appearance, such as permanent disfigurement from cancer surgery, or temporary changes in appearance, such as hair loss, that initially make the cancer survivor feel insecure and awkward. An added concern may be reduced physical stamina, which makes it difficult to meet the previous work demands and can have an impact on relationships with co-workers.

Employment Discrimination

Of paramount importance to most survivors is financial stability and the opportunity to retain their jobs during or after therapy. Yet, many who are able and willing to work encounter discrimination by being dismissed or demoted, by having benefits reduced or eliminated, or by experiencing conflict with co-workers because of a lack of understanding, ignorance, or fear about cancer (11,29,30). Hoffman (30) estimates that approximately 25% of individuals with a history of cancer experience some form of employment discrimination solely on the basis of their medical histories. Health care professionals, as well as cancer survivors, must take action on three levels to combat cancer-based discrimination: individual and group advocacy, public and professional education, and appropriate use of legal remedies (31).

Advocates hoped for legal protection against employment discrimination for qualified survivors with the passage of the Americans With Disabilities Act, but this has recently been challenged in court. Also, the Federal Rehabilitation Act of 1973 affords limited protection to those survivors whose employers receive federal funds. Most states have laws against discrimination in general, while a few states protect cancer survivors specifically. A major challenge is to test the system and file suit when discrimination is suspected.

Living with Uncertainty

Reentry may require some compromises on both the personal and the interpersonal levels. The cancer survivor may have to learn to live with physical compromises

related to the disease or to the effects of the cancer therapy. Adverse late effects of treatment may not appear for years after the completion of therapy, and the person with a history of cancer has to live with an awareness of the vulnerability associated with delayed treatment effects, recurrence of disease, or susceptibility to a second cancer. Family members also must live with these fears, and overprotectiveness by family members may be an issue after the completion of treatment. Schmale and his colleagues (32) found that 1 year after diagnosis, both survivors and family members were careful about the survivors' activity level, even when there were no obvious physical limitations.

Maintaining a Positive Future Orientation

For a while after a cancer diagnosis, the future is foreshortened, reduced to the span of time between treatments or between episodes of active disease (24), and frustration and disappointment may occur as a result of the nonlinear quality of healing (7). Cancer in the family can have a profound negative impact, and yet hopefulness and a positive future orientation are important components for quality of life in cancer survivorship. Hope is a complex concept and often is misunderstood by health care professionals. Much of the reason for this confusion is that health care professionals generally think only in terms of therapeutic hope—that is, hope that refers to a cure or remission of disease (33). Many other kinds of hope, generalized and particular, are described in the literature.

Farran et al. (34) maintain that hope is a critical clinical construct and provide the following working definition of hope (34):

> Hope constitutes an essential experience of the human condition. It functions as a way of feeling, a way of thinking, a way of behaving, and a way of relating to oneself and one's world. Hope has the ability to be fluid in its expectations, and in the event that the desired object or outcome does not occur, hope can still be present (34).

Staats and Stassen (35) define hope as a cognitive-affective resource that is a psychological asset. The purpose of hope is to guard against despair, and, as a coping strategy, it can reduce ongoing stress and discomfort quickly and for prolonged periods.

Hope is individualistic, and persons have various capacities for hoping and different approaches for maintaining hope. Individual hope is generally influenced by the patterns of hoping within the family (36).

There is a temporal aspect to hope that involves a consideration of the future, and hope changes as situations and circumstances change. Even when hope for survival is dim, individuals will find other things to hope for: pain control, mending strained relationships, or even a dignified death. Disconfirmation of one's hope usually leads to a reformulation of hope, not to its destruction (37).

Cancer survivors need and desire accurate and honest information about their disease, its treatment, and the potential side effects. They need to be aware of problems that they may have to face in the future. If these issues and concerns are presented with compassion and with assurance for continuing support, they can accept even bad news, and new, more realistic goals can be assimilated into the hoping process.

Cancer survivors are challenged to find ways to cope with uncertainty and with maintaining a positive future orientation. The fear of recurrence of cancer and heightened vulnerability may diminish over time, but the consensus is that it never completely goes away (38).

Survivor Guilt

One additional, related aspect of long-term cancer survival deserves special mention. Numerous long-term survivors express guilt over the fact that they have survived when many others have not (39). This may be a particularly salient issue for persons who have been well integrated into a support group and who have watched other members of that group succumb to their disease.

Arthur Frank, in his book *At the Will of the Body*, gives an excellent example of the concept of survivor guilt: “At the same time I was diagnosed as having cancer, a good friend my age also was diagnosed, and my mother-in-law came out of remission again. They both have died. I can make no sense of their deaths and my survival” (1).

Many survivors search for meaning and purpose in their survival and make a renewed commitment to life (40). They also may decide to try to “give something back” in practical and tangible ways. This often includes advocacy efforts on behalf of other survivors.

Living with Loss

Nothing ever prepares us for the really bad things in life, and loss is an encompassing life theme. Losses are a part of life— we lose loved ones, we lose jobs, we lose chances, and we lose dreams. There are many necessary losses when one has cancer. Some of these losses, like hair loss and loss of fertility, are physical, but emotional losses are associated with cancer as well. For example, cancer survivors may have to learn to live with some limitations, and they may have to alter goals, expectations, and hopes to fit the current, after-cancer reality.

Every loss requires a concomitant grief response or some type of mourning, but American society is uncomfortable with grief. Therefore, persons tend to hide their feelings and emotions. A secondary factor is that the person who appears to be coping well relieves others of the burden of support, so hidden grief is reinforced.

Grief, however, cannot be postponed indefinitely. It must reach expression in some way, and hidden grief may be transformed into a variety of emotional responses such as anger, guilt, anxiety, helplessness, or sadness.

The literature on the tasks of mourning is well developed (41,42). These tasks can be summarized as (a) accepting the reality of the loss, (b) experiencing the pain of the grief, (c) adjusting to a changed environment, and (d) emotionally relocating the loss in one's life and moving on.

Perhaps the most important way of helping persons experiencing loss is to “enfranchise” their grief (43). This includes recognizing their right to express emotions and encouraging them to verbalize their feelings and sadness (44). A basic step in helping people live with loss is educating them about the grief process and encouraging them to openly discuss loss issues. Through expression can come emotional healing.

REDEFINING THE CANCER EXPERIENCE

With an increasing sense of empowerment, survivors are redefining the cancer experience for themselves. For example, in 1988 the Cancer Survivors' Bill of Rights (see Appendix 75-1) was written by a survivor for the American Cancer Society. It addresses quality of life issues and identifies individual, interpersonal, and social rights to greater care and satisfaction throughout the cancer experience. Also, survivors are requesting—and sometimes demanding—that nonmedical supportive services be an integral part of cancer care and recovery. Many are working on their own to provide support, resources, and education for fellow survivors, while others are working in conjunction with health care institutions to provide these services. Survivors are joining support groups, producing publications, staffing telephone hotlines, and sharing information through online services. Others are developing community-based, mutual aid networks, are testifying before Congress, and are forming national organizations and coalitions. Advocacy—on personal, community, national, and political levels—has become a major component of the cancer care equation and is increasingly important to assure access to quality cancer care.

FINDING MEANING

Weil (45) suggests that there is no meaning to cancer—it is simply cancer. The meaning attached to the experience is different for everyone and reflects individual interpretations of the disease, treatments, and circumstances. Formulas or recipes are not enough in the assessment and care of people who are distressed and suffering. Ferrell fears that the concept of quality of life is an endangered species in today's medical and political climate and “may be lost during healthcare reform and amidst what [she has] termed the 'dehumanization' of cancer” (46). In response to this growing concern, the Texas Cancer Council outlined 10 Ethical Principles for Cancer Care (see Appendix 75-2) as the moral basis for delivering comprehensive care to people with cancer. Guidelines for action are also delineated in the complete work so that these principles can be put into practice.

The increasing needs, both biomedical and psychosocial, of this expanding population of survivors call for cooperative efforts among the recipients and providers of care, the payors who finance care, the scientists who develop better methods of care, and the politicians who set public policy as to what kind of care will be available and to whom. To ensure the integrity of our health care system, the mythology of cancer must be dispelled, caring must expand into long-term survival, and attention

must be paid to the psychosocial aspects of living with, through, and beyond cancer.

APPENDIX 75-1

CANCER SURVIVORS' BILL OF RIGHTS

The American Cancer Society presents this Survivors' Bill of Rights to call public attention to survivor needs, to enhance cancer care, and to bring greater satisfaction to cancer survivors, as well as to their physicians, employers, families and friends:

1. Survivors have the right to assurance of lifelong medical care, as needed. The physicians and other professionals involved in their care should continue their constant efforts to be:
   - sensitive to the cancer survivors' lifestyle choices and their need for self-esteem and dignity;
   - careful, no matter how long they have survived, to have symptoms taken seriously, and not have aches and pains dismissed, for fear of recurrence is a normal part of survivorship;
   - informative and open, providing survivors with as much or as little candid medical information as they wish, and encouraging their informed participation in their own care;
   - knowledgeable about counseling resources, and willing to refer survivors and their families as appropriate for emotional support and therapy which will improve the quality of individual lives.
2. In their personal lives, survivors, like other Americans, have the right to the pursuit of happiness. This means they have the right:
   - to talk with their families and friends about their cancer experience if they wish, but to refuse to discuss it, if that is their choice and not to be expected to be more upbeat or less blue than anyone else;
   - to be free of the stigma of cancer as a “dread disease” in all social relations;
   - to be free of blame for having gotten the disease and of guilt for having survived it.
3. In the workplace, survivors have the right to equal job opportunities. This means they have the right:
   - to aspire to jobs worthy of their skills, and for which they are trained and experienced, and, thus, not to have to accept jobs they would not have considered before the cancer experience;
   - to be hired, promoted, and accepted on return to work, according to their individual abilities and qualifications, and not according to “cancer” or “disability” stereotypes;
   - to privacy about their medical histories.
4. Since health insurance coverage is an overriding survivorship concern, every effort should be made to assure all survivors adequate health insurance, whether public or private. This means:
   - for employers, that survivors have the right to be included in group health coverage, which is usually less expensive, provides better benefits, and covers the employee regardless of health history;
   - for physicians, counselors, and other professionals concerned, that they keep themselves and their survivorclients informed and up-to-date on available group or individual health policy options, noting, for example, what major expenses like hospital costs and medical tests outside the hospital are covered and what amount must be paid before coverage (deductibles);
   - for social policy makers, both in government and in the private sector, that they seek to broaden insurance programs like Medicare to include diagnostic procedures and treatment which help prevent recurrence and ease survivor anxiety and pain.

Adapted from Spingarn ND. *The cancer survivors' bill of rights.* Atlanta, GA: American Cancer Society, 1988, with permission.

APPENDIX 75-2

ETHICAL PRINCIPLES FOR CANCER CARE

I. Since cancer affects a person's entire sense of well-being, cancer care cannot be equated with or limited to prevention, early detection, and treatment of bodily disease. To deal with the effects of cancer, this care should address humans as whole persons with biological, emotional, social, economic, informational, moral, and spiritual needs.
II. Benefiting persons with cancer is the highest priority of health care professionals. Individuals fully benefit when they receive personalized, comprehensive, coordinated, and culturally sensitive care.
III. Patients are to be respected as autonomous, self-governing persons with the right to express their needs and emotions and make informed decisions in their own best interests.
IV. To make informed decisions, patients must be provided with information that is understandable, sufficient, and applicable to their circumstances.
V. Effective communication is essential in order to benefit persons with cancer and respect their autonomy. This communication rests on trust, concern, mutual respect, honesty, and self-awareness.
VI. Terminally ill patients are to receive continued health care, support, respect, and assurance.
VII. Collegial teamwork is essential for attending to the total human dimensions of cancer care.
VIII. Teamwork is sustained by caregiver collegiality, which is based on a mutual understanding of and respect for the individual and professional contributions of colleagues.
IX. The ability of health care professionals to care for patients and those close to the patient depends on caregivers attending to their own personal, psychological, social, moral, and spiritual needs.
X. Basic, clinical, and psychosocial research is integral to improving cancer prevention, early detection, diagnosis, treatment, long-term followup, and the personal dimensions of cancer care. All research should contribute to, not detract from, beneficial and respectful care of individuals with cancer.

From Vanderpool HY, ed. *The human dimensions of cancer care: principles and guidelines for action*. Galveston: The Texas Cancer Council and Institute for the Medical Humanities, The University of Texas Medical Branch at Galveston, 1994. Copyright 1994, Texas Cancer Council, with permission.

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76

PALLIATIVE CARE IN PEDIATRICS

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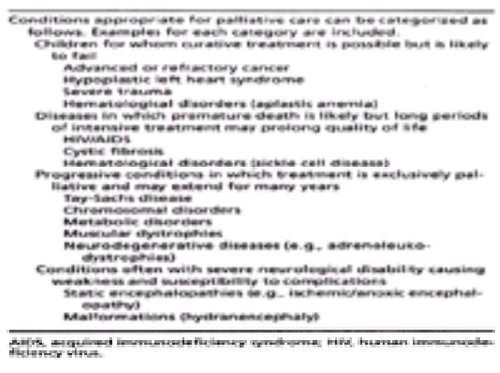
BRUCE P. HIMELSTEIN

PEDIATRIC PALLIATIVE CARE

As defined by the World Health Organization, palliative care is compassionate and all-inclusive care when curative treatment is no longer possible. This care addresses physical, spiritual, emotional, and psychological needs of the dying (1). More broadly, palliative medicine for children is the art and science of family-centered care aimed at enhancing quality of life and minimizing suffering. Cassel eloquently defined *suffering* as “the state of severe distress associated with events that threaten the intactness of the person” (2). Inherent in this definition is the possibility of delivering palliative care in partnership with curative care for children with life-limiting illness or for children who may not die. Many principles already reviewed in other sections of this book are universally applicable across the age spectrum of the dying, so this chapter provides an overview of issues specific to the care of the life-threatened child.

The overall improvement in the health of Americans over the 20th century is best exemplified by a dramatic decline in age-adjusted death rates and an increased life expectancy (3). The impact of scientific and technological advances in modern medicine is evident in the notorious drop in childhood mortality rates from all causes and a shift from infectious illnesses to chronic disease and trauma as the primary causes of death in children. This shift in the morbidity and mortality of pediatric diseases calls for an ever-increasing attention to palliative care issues for seriously ill children and their families. In 1998, over 20,000 infants and 26,000 children ages 1 to 19 years died in the United States (4), many of them experiencing long, protracted illnesses associated with substantial pain, and emotional and spiritual challenges.

Although cancer is the most common cause of nontraumatic death in children in the United States, and approximately one-third of children with malignancy still die in economically advantaged areas of the world, there are many other diseases for which palliative care is appropriate. Using a broad definition of advanced illness, the diseases of childhood which might be appropriate for palliative care might include those outlined in Table 76-1; it should be noted that this definition falls well outside of the scope of traditional hospice care, as defined in the United States Medicare Hospice Benefit.



Conditions appropriate for palliative care can be categorized as follows. Examples for each category are included.
- Children for whom curative treatment is possible but is likely to fail
  - Advanced or refractory cancer
  - Hypoplastic left heart syndrome
  - Severe trauma
  - Hematological disorders (aplastic anemia)
- Diseases in which premature death is likely but long periods of intensive treatment may prolong quality of life
  - HIV/AIDS
  - Cystic fibrosis
  - Hematological disorders (sickle cell disease)
- Progressive conditions in which treatment is exclusively palliative and may extend for many years
  - Tay-Sachs disease
  - Chromosomal disorders
  - Metabolic disorders
  - Muscular dystrophies
  - Neurodegenerative diseases (e.g., adrenoleuco-dystrophies)
- Conditions often with severe neurological disability causing weakness and susceptibility to complications
  - Static encephalopathies (e.g., ischemic/anoxic encephalopathy)
  - Malformations (hydranencephaly)

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

TABLE 76-1. CRITERIA FOR PALLIATIVE CARE

There is little substantive data to assist in determining the potential scope of practice for children with palliative care needs worldwide. In England, Goldman estimated that 50,000 to 100,000 children are living with life-threatening illness. In parts of the world where medical care may not be as readily accessible as in highly developed countries, the scope of practice might be significantly larger (5).

Epidemiology of Suffering

Despite best efforts, children living with chronic, life-threatening, and terminal illnesses experience substantial suffering. This experience of serious disease is multidimensional. It has broad-ranging implications in the child's life as a whole and in the family as a functional unit. Suffering results from a threat to one's physical and psychological self, from a threat to one's relationships with others, and from a threat to one's relationship with a transcendent source of meaning (6). Suffering is a profoundly personal experience and is endurable, and at times even fulfilling, when it becomes meaningful (7).

Within the physical realm, the published experience speaks best to those with malignant diseases. Recent studies by Wolfe (8) and Collins et al. (9) point to the wide variety and high prevalence of symptoms from which children suffer with life-threatening illness, including fatigue, nausea, pain, dyspnea, anorexia, constipation, and diarrhea, just to name a few. Furthermore, currently available treatments may not be successful in easing suffering associated with these symptoms that can cause significant distress. The work of Wolfe also demonstrates significant discrepancies between the reports of parents and physicians regarding the children's symptoms in the last month of life, with parents reporting each symptom more than the physicians.

For children with nonmalignant diseases, some of the more troublesome symptoms might include gastroesophageal reflux, neuroirritability, immobility, incontinence, seizures, muscle spasms, pressure ulcers, contractures, recurrent infections, increased secretions, restlessness, sleep disturbance, and edema. There are few valid and reliable tools available to assess these symptoms and little data to substantiate the use of many of the interventions currently prescribed. Equally important is the need to recognize the role that health care providers have in contributing to the overall experience of suffering for patients and families, particularly when the emphasis is placed on life prolongation and the use of aggressive medical procedures and other painful interventions in realistically futile situations.

Serious illness threatens children's sense of personal integrity and shatters all aspects of their lives. Physical pain and other symptoms cause fear, depression, and isolation. Illness affects their daily activities, sense of well-being, physical strength and agility, and the motives and quality of their relationships. Disease crushes their

sense of security, and brings fears of the unknown, rejection, and punishment. Children also become confused by the experience of a mixed variety of emotions of anger, anxiety, sadness, loneliness, and isolation in the presence of a threatening situation (10). Children are highly vulnerable to the stress inherent to the experience of severe illness. They have an egocentric view of the world and lack a fully developed repertoire of coping mechanisms, such as problem solving or decision making, which are influenced by age-dependent behavior and cognitive abilities.

Suffering, for the parents of a child with a life-threatening illness, can be a multidimensional experience of pain, fear, failure, despair, powerlessness, hopelessness, purposelessness, and vulnerability. These experiences are both personal and interpersonal. Parental anxiety is due in part to the changing parent-child structure, the need to understand the illness experience, become familiar with the hospital environment, adapt to the changing relationships with their child and other family members, and negotiate with professionals about their care (11,12). Parents must also deal not only with the immediate threat of disease on their child's life, but also with important additional family stressors during treatment such as lifestyle changes, marital tension, financial strain, loss of self-esteem, and even loss of sleep (13,14 and 15). Furthermore, when confronted with the suffering and possible death of their child, parents frequently recognize their own limitations and mortality. Their perception of life, death, and the world around them is changed dramatically by the reality of the loss of their child, a loss that involves not only a loved family member, but also the future embodied in the hopes and dreams that were invested in the child (16). In addition, parents must also satisfy the emotional needs of other children in the family which many times parallel those of the seriously ill child (17). Finally, children and their families may also suffer spiritually. This may be manifested as a sense of isolation and abandonment, a sense of hopelessness and uncertainty about the meaning and ultimate purpose of life.

Barriers to Pediatric Palliative Care

Poor symptom control is only one of many barriers to access to good palliative care. Most important in pediatrics, hopes for peaceful dying, comfort, lack of suffering, and escalating engagement with caregivers are often lost in the wish to maintain life at any cost, as death in childhood defies the natural order. Moreover, the gradual transition from curative therapy to comfort as the primary goal of care is marked by uncertainty, the decision points are ambiguous, and the process is painful and difficult for all involved. Additional barriers to access for palliative care that enhance suffering and degrade quality of life for lifethreatened children are outlined in Table 76-2.

Rarity of death in childhood
Inexperience of personnel providing pediatric palliative care
Differences between children and adults and their diseases
Defiance of the natural order when children die
Provider sense of failure when a child dies
Immeasurable parental distress at loss of child
Inability to predict time of death
Requirement for "do not resuscitate" orders
Inadequate education for providers and families about palliative care
Association of palliative care with "giving up" and "hopelessness"
Fragmentation of medical and psychosocial/spiritual services for children
Poor reimbursement for time and labor-intensive, bio-behavioral palliative care
Difficulty of death communication across chronological and developmental ages
Lack of symptom assessment tools
Lack of pharmacokinetic data for children taking symptom relief medications

TABLE 76-2. BARRIERS TO ACCESS FOR PEDIATRIC PALLIATIVE CARE

Models of Care Delivery

The American Academy of Pediatrics supports an integrated model of palliative care in which the components of palliative care are offered at diagnosis and continued throughout the course of illness, whether the outcome ends in cure or death (18). The basic principles necessary to provide compassionate pediatric palliative care are outlined in Table 76-3. In different socioeconomic arenas, reviewed in the Compendium of Pediatric Palliative Care (19), many different approaches to palliative care service delivery might be successful. These essentials do not mandate a particular structure for care delivery other than to suggest the function of an interdisciplinary team of health care and allied health care professionals to provide care coordination and to facilitate the delivery of services with the goal to minimize suffering and improve quality of life. As shown in Figure 76-1, care coordination can bridge the gaps between traditionally defined supportive care (part of active disease treatment), active palliative care, traditionally defined hospice (end-of-life) care, and bereavement.

Care is child-focused, family-oriented, and relationship-centered.
Care focuses on relief of suffering and enhancing quality of life for the child and family.
All children suffering from chronic, life-threatening, and terminal illnesses are eligible.
Care is provided for the child as a unique individual and the family as a functional unit.
Palliative care is incoporated into the mainstream of medical care regardless of the curative intent of therapy.
Care is not directed at shortening life.
Care is coordinated across all sites of care delivery.
Care is goal directed and is consistent with the beliefs and values of the child and his or her caregivers.
An interdisciplinary team that is always available to families to provide continuity delivers care.
Advocacy for participation of the child and caregivers in decision making is paramount.
Facilitation and documentation of communication are critical tasks of the team.
Respite care and support are essential for families and caregivers.
Bereavement care should be provided for as long as needed.
"Do not resuscitate" orders should not be required.
Prognosis for short-term survival is not required.

TABLE 76-3. BASIC PRINCIPLES OF PEDIATRIC PALLIATIVE CARE

FIGURE 76-1. Advanced illness care coordination.

Advanced Care Coordination

Much of the fragmentation of services that occurs in modern health care systems results from the lack of a coordinating entity. The loss of continuity may be addressed by providing a medical home for these children along with the services of an advanced-illness care coordinator. This may be a registered nurse whose primary responsibilities are to enhance communication across settings, facilitate the participation of the patient and family in the decision-making process, ensure that health care providers adhere to the goals and principles of palliative care, and honor the patient and family's wishes. The coordinator may also be responsible for ensuring access to proper management of pain, and psychosocial and spiritual support. The advanced-illness care coordinator may advocate for change in the nature of the palliative care interventions according to the stage of disease and the patient and family's expectations, values, and beliefs. In our experience, provision of a trained, advanced-illness care coordinator to facilitate end-of-life communication also increases utilization of and length of stay in end-of-life services and completion of advance directives. The roles provided by a physician advocate and the integration of services facilitated by the advanced care coordinator are essential for

maintaining a patient-focused, relationship-centered approach and promotion of palliative care goals.

Goals of Care

In the provision of palliative care, assessment of the goals of care is paramount to avoid unnecessary physical and emotional suffering (20). Painful procedures and other medical interventions should be recommended in the palliative care of seriously ill children only after all alternatives have been considered and the goals of care are defined in a way that is consistent with the beliefs and values of each family. Palliative care should be offered for all children suffering from serious illness. However, the relative priority of the goals of medical care is influenced by many factors, including past experiences, the child and family's perceptions of the severity of the illness, prognosis, and whether or not the illness progresses and the patient is approaching death. Physicians have been trained to cure, and many times losing a patient to progression of disease is perceived as a failure. Consequently, it is frequently difficult for physicians, particularly for those caring for children, to let go of the need to “succeed” in the cure of disease when treatment appears to be futile. When a child is diagnosed with a serious illness, the focus is mostly on the illness and its treatment, guided by what science dictates as the most effective therapy to restore bodily function. The goal to restore function is progressively less important as the disease progresses and death appears closer. The experience of living with a terminal illness grows to be more personal and subjective, and the need to have a sense of integrity and wholeness becomes essential. The process involves a gradual and seamless transition from the time of diagnosis to the time of death. Supportive care services must be offered at the time of diagnosis, when treatment with aggressive curative intent is given. When cure is no longer a realistic goal, palliative care interventions may be offered to prolong a life of good quality. When the illness becomes terminal, palliative care can be provided through programs that focus on end-of-life care at home if consonant with the family's wishes. Finally, grief and bereavement counseling should be offered to family members before and after the child dies.

Of note, the use of complementary and alternative medicine to treat chronic illness or disability in children is increasing. Although some alternative medicine practices may be justified, particularly for illnesses that impose a heavy burden of suffering for which mainstream therapies are insufficient, there are no published guidelines for the use of these practices in children (21). In the case of vulnerable children suffering from serious illness, parents may be willing to try a variety of approaches hoping for benefit in a desperate situation, some of which may be potentially harmful (22). To best serve the interests of children, physicians must maintain a scientific perspective, provide balanced advice about therapeutic options, and establish or maintain a trusting relationship with families (23). The management and maintenance of hope in these circumstances is of utmost importance.

Ethical Issues

Shared decision making in pediatrics, driven by communication between child, parent, and physician, defines the standard in medical ethics. Judgments that relate to withholding and/or withdrawing certain therapies, as well as judgments concerning futile medical interventions, are essentially subjective but realistically indispensable (24). There is marked variability among physicians regarding the use of artificial life support, but in general, decisions must be goal directed and in consonance with the child's and family's beliefs and values (25). Maintaining open and honest communication and continuity of care is essential. The decision to discontinue life-support measures should be carried out in the most compassionate and practical way. In conversations with the parents, one must consider the prognosis for recovery, the goal that is being pursued, the quality of the life that is being prolonged, and whether or not the child is experiencing suffering or is permanently unaware of self and his or her surroundings. Advanced care planning for the child with life-limiting illness must include discussions regarding withholding and/or withdrawing of artificial lifesustaining therapies, such as cardiopulmonary resuscitation, mechanical ventilation, and medically provided artificial hydration and nutrition, or other interventions that may potentially prolong life such as chemotherapy, antibiotics, and transfusion of blood products. Discussions regarding establishment of “do not resuscitate” orders should occur in the context of a general approach to minimize suffering and improve quality of life rather than as an isolated plan to discontinue an intervention unrelated to the child's overall experience. Each drug, intervention, or treatment should be assessed in terms of beneficence (to do good) and nonmaleficence (to do no harm) (26).

Withholding and withdrawing artificial, life-sustaining interventions in children, particularly medically provided artificial hydration and nutrition, is often controversial. However, if there is insufficient justification for continued treatment when it is determined with a high degree of certainty that the patient has no hope of regaining some potentiality for function and human relationships, withdrawal of treatment is appropriate (27). As with adults, there is no ethical obligation to continue life-sustaining therapy for children when there is no therapeutic benefit other than to prolong life or if no goals of medicine are obtained such as improving health and quality of life, restoring function, or relieving pain and suffering (28). Discontinuation of nonbeneficial interventions is squarely within the scope of parental, decision-making authority for their child and is not inconsistent with the child's best interests. Although children are allowed to assent rather than to consent to plans regarding their care, parents and health care providers must recognize the subjective personal nature of suffering and respect the child's autonomy and capacity to make decisions, particularly for emancipated and mature minors (29). Whenever possible, caregivers must make an effort to invite children to participate in medical decision making and honor their end-of-life care wishes. This is particularly important for any child, regardless of age, who can understand his or her medical condition, who can communicate his or her preferences, and who is able to reach a reasonable decision and can understand its consequences. In addition, the principles that guide the rule of double effect and sedation of highly symptomatic patients with pain or dyspnea in adults also apply in the care of children (30,31). In difficult cases, institutional ethics committees can help resolve conflicts about treatment decisions, provide a forum for discussion of hospital policies, and educate the health care community about ethical concepts (32).

SYMPTOM CONTROL

This section briefly addresses management of the most common symptoms. Several outstanding and more comprehensive resources are available for pain management in children (33,34,35 and 36).

Pain Assessment and Management

Pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (37). It is subjective in nature.The experience of pain can be modulated by environmental, developmental, behavioral, psychological, familial, and cultural factors. Unrelieved pain for the child can produce fear, mistrust, irritability, impaired coping, and posttraumatic stress symptoms. Parents feel guilt and anger when pain is undertreated. Many children have pain at some time during their course with lifethreatening illness; it can be disease related, treatment related, and/or related to psychological distress (38). Incidental, or traumatic pain, can still occur in a life-threatened child as well.

Pain assessment must be age-appropriate and requires a careful history and physical examination, determination of the primary cause(s) of pain, and evaluation of secondary causes and modulating features. Pain complaints should always be taken seriously; severe pain for a child is a medical emergency.

Elements of the pain assessment should include the quality of the pain, region and radiation, severity, temporal factors, and provocative and palliative factors. Additional historical elements include disease stage and context, fear of pain, ability to take medication, prior analgesic use, potential role of disease-specific treatment, reactions of parents and family context, and other nonpain symptoms, including depression and/or anxiety, sleep disturbance, and most important, interference with activities of daily life, including play.

Methods of pain assessment must be appropriate to the child's age, situation, emotional resources, developmental level and context, and wishes of the child and family. Ideally, pain assessment, being subjective, should be by self-report. For children >7 years of age, visual analogue or verbal response scales are appropriate. For children ages 3–7, several validated, self-report tools are available, including Faces Scale (39), Oucher (40), poker chip tool (41), body maps, and pain thermometers (42,43). For infants, toddlers, and preverbal children, several behavioral assessment scales exist, including CRIES (44), the Neonatal Infant Pain Scale (45), and CHEOPS (46). Collins et al. (9) have recently published a tool that can be used to measure a variety of symptoms in children with cancer 10 to 18 years of age without cognitive impairment. A tool to measure symptoms among children ages 8 to 13 years is in preparation by the same group. The International Association for the Study of Pain has published an excellent review of pain assessment in children (47).

In general, pain management for children should follow the World Health Organization analgesic ladder (48). Table 76-4 lists some of the more commonly used and available medications for mild, moderate, and severe pain. Particularly for children who cannot swallow pills, the long half-life, low cost, and availability in concentrated liquid formulation make methadone a good choice for long-term analgesia (49). A short initial and long terminal half-life requires judicious titration to prevent oversedation. Given toxic metabolite accumulation and the availability of several alternatives, meperidine cannot be recommended and is excluded from the table.

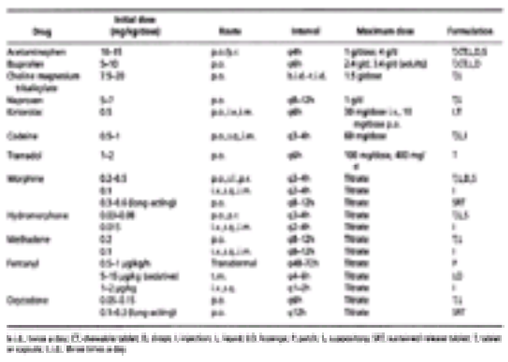


TABLE 76-4. OPIOID AND NONOPIOID ANALGESICS

Medications for pain should be administered according to a regular schedule; “p.r.n.,” “as needed,” and “reverse p.r.n.” dosing requires that children first experience pain before they can receive medication. Rescue doses should be provided for intermittent or more severe breakthrough pain. Expert anticipation, prevention, and treatment of medication side effects are critical.

Depending on the etiology of pain being treated, there are many nonopiate adjunct therapies available. Table 76-5 lists some of the more commonly used medications and their indications.

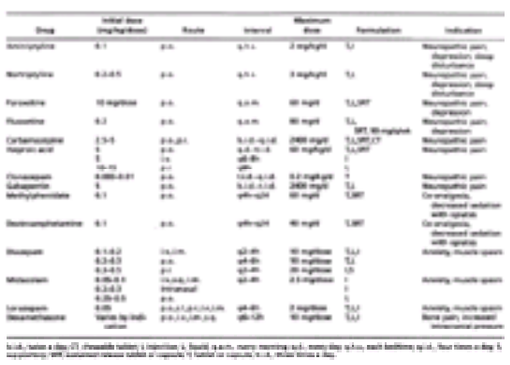


TABLE 76-5. ADJUVANT DRUGS USEFUL IN PEDIATRIC PAIN MANAGEMENT

For children in particular, choose the simplest, most effective, least painful route which for most children will be oral or sublingual, or for those with central venous access, parenteral. Intramuscular injections should be avoided if possible. Rectal administration is possible, and many medications, including nonopiates and opiates as well as medication for nonpain symptoms, can be absorbed rectally. Subcutaneous infusion, popular in adult hospice and palliative medicine, is possible in children but may be inadvisable for needle-phobic children. Transdermal and inhalational routes may also be used in children, but little pharmacokinetic data is available regarding their use; anecdotally, absorption and/or metabolism of transdermal fentanyl may be faster in children, requiring patch changes every 2 days if breakthrough pain occurs.

Promotion of good psychosocial and spiritual care must be partnered with appropriate pharmacology. Children should be given choices as often as possible. Behavioral methods, such as deep breathing (blowing bubbles), progressive relaxation, and biofeedback, have a role in pain management for children. Physical methods, such as touch therapies, including massage, transcutaneous electrical nerve stimulation, physical therapy, heat/cold, and acupuncture and/or acupressure, for example, are helpful adjuncts. Cognitive modalities, including distraction, music, art, play, imagery, and hypnosis, are also effective in children. Studies have demonstrated efficacy of many of these modalities alone or in combination with pharmacological therapies (50). These therapies should be approached from a familycentered perspective; parents can easily be taught many of these techniques. Providing effective tools for parental involvement in symptom management should increase feelings of control in an often uncontrollable situation.

Respiratory Symptoms

Shortness of breath, “air hunger,” and dyspnea, the subjective sensation of not being able to catch one's breath, are potentially distressing and frightening to children and parents alike. In children, there are many potential causes, but the major contributors are space-occupying lesions, such as metastatic tumor or tumor-associated effusions, infectious processes, such as aspiration or acquired pneumonia, and finally, severe skeletal or neuromuscular abnormalities which impede normal respiratory excursion.

The assessment of these symptoms relies heavily on objective measures, such as respiratory rate or transcutaneous oxygen saturation, but, except for maximal inspiratory pressure, these measures, as well as more complex pulmonary function measures, do not necessarily correlate well with the subjective sensation of dyspnea (51). There are some validated visual and numeric dyspnea scales for the assessment of breathlessness in adults (52,53). Pianosi et al. (54) have begun to validate a pictorial tool to assess breathlessness in children that should assist investigators attempting to conduct clinical trials of interventions for dyspnea.

Treatment modalities for dyspnea depend on the disease stage and progression, proximity to death, and patient/family context. Dyspnea, given its association with severe distress, should be treated promptly and aggressively. Specific measures aimed at the underlying pathology should always be considered, for example, drainage of effusions, treatment of pneumonia, or chemoradiotherapy or surgical extirpation for pulmonary metastases. For symptomatic relief, combination therapy with oxygen, oral or parenteral opiates and/or benzodiazepines should be considered without concern regarding potential for respiratory suppression (55). Although many hospice and palliative care specialists advocate the use of inhaled or nebulized opiates, there are no randomized clinical trials to clearly prove their benefit (56).

Gastrointestinal Symptoms

Children with chronic and serious diseases often have gastrointestinal complaints. Nausea and vomiting are among the most common gastrointestinal symptoms seen in children and cause significant distress and diminish function and quality of life. Assessment of nausea is difficult in the young child who may lack the cognitive abilities to distinguish the symptom and express his or her experience verbally. Nausea in these children may manifest as inactivity, weakness, irritability, and poor appetite. In older children, self-report is the preferred method of assessment. Nausea and vomiting may be secondary to gastrointestinal illness such as gastroenteritis, constipation, gastric stasis, ileus, peritoneal irritation, pancreatitis, obstruction, appendicitis, food poisoning, or overfeeding. Neurological causes of nausea and vomiting include increased intracranial pressure secondary to brain tumor, subdural hemorrhage, or obstructive hydrocephalus. Middle ear disease or some brain tumors may cause nausea and vomiting from stimulation of the vestibular pathway. Certain medications, including chemotherapy, narcotics, antibiotics, nonsteroidal anti-inflammatory agents, and anticholinergics can cause severe nausea and vomiting. Systemic infections as well as other illnesses, such as congenital adrenal hyperplasia, inborn errors of metabolism, and Reye's syndrome, among others, can also present with emesis. Anticipatory nausea and vomiting may reflect the presence of anxiety and stress. Postoperative nausea and vomiting is also a common occurrence in children.

The presence of nausea and vomiting calls for immediate action on the part of the caregivers. Identification of the source of these symptoms is important to select appropriate therapy. Management of nausea and vomiting in children is the subject of a recent review (57). Table 76-6 lists some of the antiemetics used in the treatment of children. Prokinetic agents, such as metoclopramide and cisapride, are useful in the treatment of ileus and intestinal hypomotility. Cisapride can cause arrhythmias, particularly in children receiving antifungal therapy. Antihistamines (e.g., diphenylhydramine, dimenhydrinate, meclizine), phenothiazines (e.g., promethazine, chlorpromazine), and butyrophenones (e.g., haloperidol) are useful in the treatment of centrally mediated nausea and vomiting as in increased intracranial tumors or vestibular stimulation but are also good antiemetics for patients with gastrointestinal disease. Ondansetron and granisetron are 5-HT3 antagonists and the treatment of choice in chemotherapy and radiation therapy–induced and postoperative nausea and vomiting. In patients receiving highly emetogenic chemotherapy, these medications must be used as part of an aggressive antiemetic regimen (58). Corticosteroids have intrinsic antiemetic properties and potentiate effect of other antiemetics. Cannabinoids have antiemetic properties, as well, but its use in pediatrics is limited. Synthetic cannabinoid preparations are also

available and may be helpful in severe cases. Benzodiazepines may reduce anxiety and the likelihood of anticipatory nausea. Nondrug measures for palliation of nausea and vomiting that may enhance the effect of antiemetic drugs include acupuncture, psychological techniques, and transcutaneous electrical nerve stimulation (59).

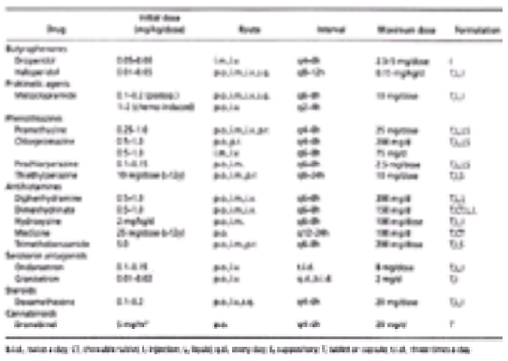


TABLE 76-6. ANTIEMETICS

Constipation, defined as the passage of small hard feces infrequently and with difficulty, is a common complaint among pediatric patients (60). Constipation is a self-perpetuating problem in children. Hard stools are difficult and painful to evacuate, and that may lead to a vicious cycle of constipation. In the child with severe constipation, encopresis may be mistaken by diarrhea. On physical examination, clay-like masses may be palpated in a partially distended abdomen and hard stools may be palpated on rectal examination. Opioids, vincristine, and drugs with anticholinergic effects, such as phenothiazines and tricyclic antidepressants, may cause constipation. Other causes include malignant intestinal obstruction and metabolic conditions such as dehydration, cystic fibrosis, hypothyroidism, and hypercalcemia. Spinal cord injuries or other neuromuscular illnesses may be associated with constipation as well.

As in adults, prophylactic measures are the first line of intervention (61). Children, particularly older school-age patients and adolescents, should be encouraged to remain as mobile as possible. Adequate fluid intake and increased fiber in the diet are helpful. Drugs that cause constipation may be discontinued or a laxative may be added to the regimen. Also, children must be encouraged to attempt defecation after meals to take advantage of the gastrocolic reflex. Hospital staff must allow children privacy for defecation and, whenever possible, the use of a commode or lavatory rather than a bedpan should be encouraged. Treatment of constipation in children includes a variety of oral laxatives and/or enemas. The selection of laxatives can be made by considering modes of action of available agents. Patients with hard stools can receive laxatives with predominately softening action such as mineral oil, lactulose, or docusate sodium. If on physical examination the rectum is full of soft feces, a predominantly peristalsis-stimulating agent such as senna or bisacodyl may be indicated. Osmotic laxatives, such as polyethylene glycol or magnesium citrate, and rectal laxatives, such as glycerin suppositories, sodium docusate, or sodium phosphate enemas, can also be used in symptomatic children with severe constipation. Maintenance therapy may be necessary for patients with chronic constipation. The use of laxatives in these patients does not lead to dependence. Mineral oil does not cause malabsorption of fat-soluble vitamins and may be used in children as part of a maintenance regimen but should be avoided in neurologically impaired children at risk of bronchoaspiration. More recently, glucomannan, a soluble fiber, has been recommended for the treatment of constipation in the neurologically impaired child (62). Among the nonpharmacologic interventions, biofeedback may be potentially useful in children (63).

Diarrhea, one of the most common problems encountered by pediatricians, is defined as the passage of frequent, loose stools. Viral, bacterial, and parasitic infections are among the most common causes of acute diarrhea. Most patients with acute diarrhea have viral gastroenteritis, especially if stools are watery and do not contain either blood or mucus. Patients with fever, abdominal cramps, and/or bloody stools most likely have dysentery syndrome and should be treated empirically with trimethoprim/sulfamethoxazole while awaiting results of culture and bacterial susceptibility (64). Diarrhea persisting for longer than 3 weeks is said to be chronic and may be linked to serious organic noninfectious diseases such as anatomical defects, malabsorption syndromes, endocrinopathies, and neoplasms.

Dehydration is particularly common in young children with diarrhea and vomiting. Aggressive, prophylactic treatment with hydration solutions (e.g., Pedialyte) and careful follow-up are paramount to prevent serious complications. Kaolin and pectin may be useful adjuncts in the treatment of diarrheal illness in children. Products containing salicylates (e.g., bismuth subsalicylate) should be avoided in children. Probiotics (e.g., lactobacillus species) have been used in the treatment and prevention of antibiotic-associated diarrhea, preventing relapse of *Clostridium difficile* infections, and as an adjunct to rehydration therapy, but their use in children remains controversial (65,66).

Gastroesophageal reflux is particularly common in children with neurological impairment, some of whom may require surgical fundoplication to reduce symptoms and decrease the risk of aspiration pneumonia. Useful medications include aluminum hydroxide with or without magnesium hydroxide, calcium carbonate, and H_2-receptor blockers such as ranitidine. Prescription proton pump inhibitors (e.g., omeprazole or lansoprazole) for children with gastroesophageal reflux and peptic ulcer disease continue to increase as clinicians become more aware of their range of action and safety profile (67).

For patients experiencing cachexia as a result of prolonged, chronic childhood diseases, megestrol acetate, a synthetic progesterone derivative, appears promising as an agent to reverse the growth failure observed in these patients (68). Cyproheptadine can be used as an appetite stimulant in children. Corticosteroids and cannabinoids may also have a therapeutic role. However, anorexia and cachexia are often a normal part of the dying process; appropriate patient and family counseling about this fact may reduce distress and obviate the need for therapeutic intervention with medication or with artificial hydration and nutrition.

Pruritus

Pruritus, defined as any stimulus that promotes scratching, may be multifactorial in children but is most commonly related to dry skin or to medication side effects, in particular opiates. As for many other childhood symptoms, there are no standardized assessment tools for pruritus other than the telltale physical signs, including excoriation, lichenification, and/or erythema, as well as behavioral clues such as rubbing of eyes, nose, and/or other skin surfaces. Treatment depends upon the cause; topical therapy with moisturizers and emollients may ameliorate itching associated with dry skin. Systemic corticosteroids may be effective for the often severe pruritus associated with progressive lymphomas. For drug-induced pruritus, modification of the drug regimen is the best therapy. If children must be maintained on a medication associated with pruritus, appropriate pharmacotherapy should be instituted, including antihistamines or partial opiate antagonists such as nalbuphine. Doxepin may also be used enterally or topically. Although attractive options for other indications, nonsedating antihistamines, such as loratadine, may be less effective for pruritus.

Bone Marrow Failure

Bone marrow failure can result in significant suffering and diminution of quality of life for children. It is most often the result of primary malignancy, such as leukemia or neuroblastoma in the bone marrow, or due to the toxic effects of medications. Progressive anemia and resultant fatigue, leukopenia, and its associated risk of infection, and thrombocytopenia and its associated risk of bleeding, may significantly impact upon the ability of the child to participate in play and school, the critical activities of the child.

Treatment decisions should primarily be made in consideration of the child's quality of life. Some children with progressive leukemias, for example, can be maintained with excellent quality of life with a combination of palliative chemotherapy with blood product support and expectant treatment of infectious complications. Oral chemotherapeutics, such as etoposide, Cytoxan, hydroxyurea, or antimetabolites, as well as phase agents, may have a role in such a care plan. Conversely, such support may not be appropriate for a child with protracted bleeding, severe infection, or other complications of end-stage bone marrow failure that significantly impair quality of life. Comfort and prevention of suffering should be optimized regardless of the level of overall support and intent to prolong meaningful life.

For anemia, red cell transfusions to keep the hemoglobin above 7 g/dl may be beneficial. One must weigh the relative increase in risk of thrombocytopenic bleeding, however, at very high hemoglobins. For thrombocytopenia, prophylactic platelet infusions to keep the platelet count above 10,000/mm^3 may be appropriate; clinical titration with scheduled infusions may be easier on the child and family. Gentle oral hygiene with soft toothettes is necessary. Agents to treat mucosal bleeding should be available in the home. Aminocaproic acid, tranexamic acid, desmopressin, and topical thrombin may all have a role. Families should be prepared for the possibility of severe bleeding with appropriate opiates, sedatives, and darkly colored towels to absorb blood.

For neutropenic patients or other patients at risk of infections, such as aspiration pneumonia, decisions need to be made proactively regarding use or nonuse of antimicrobial therapy. For immunocompromised patients with central catheters, and depending upon the availability of home services, blood culture bottles and antibiotics tailored for ease of use and broad coverage such as ceftriaxone or ciprofloxacin can be stored in the home to be used as needed. For children at risk for aspiration, the authors often keep a supply of unreconstituted powder or tablet form of antibiotics, such as amoxicillin/clavulanic acid or azithromycin, for empiric

treatment at onset of fever and/or respiratory distress. Again, parents must be well aware of the risks of treatment failure, including death, in these clinical scenarios.

Genitourinary Symptoms

Retention of urine in children is most often a side effect of anticholinergic medications, in particular opiates, antihistamines, direct anticholinergics, such as hyoscyamine or scopolamine, or tricyclic antidepressants. Urinary infection can also mimic drug-induced retention. Particularly in a nonverbal child or in a child with fever, assessment of urinalysis and culture may be appropriate to rule out infection unless a more obvious source can be found. In children with malignancy, changes in urination may be a sign of incipient spinal cord compression; careful history and neurological assessment should be performed if there is suspicion. Dehydration may also mimic urinary retention, but there are typically other obvious physical signs and symptoms to suggest this diagnosis. Finally, chemotherapy and radiation therapy may be associated with both immediate and long-term sequelae on the bladder and urinary system. For example, hemorrhagic cystitis from alkylating agents can recur months or years from treatment, sometimes in the setting of intercurrent viral illness.

Therapeutically, conservative measures, such as warm compresses or gentle pressure to the bladder and ambulation, if possible, may be effective. Reversal of drug-induced urinary retention may be accomplished most often by changes in medications; occasionally cholinergics, such as bethanechol or opiate antagonists, may be helpful adjuncts. When these maneuvers fail, clean catheterization may be required. Depending upon proximity to death, mobility, and patient/family preference, indwelling catheterization may be preferable to clean intermittent catheterization when outlet obstruction is anticipated to be prolonged.

Fatigue

Fatigue is among one of the most prevalent symptoms in children dying with cancer (8,9). It is a nonspecific symptom that is difficult to measure and describe due to its subjective nature and the lack of confirmed physiological and laboratory indicators (69). Symptoms of fatigue may include physical weakness, mental exhaustion, disruption of sleep, reduced energy, emotional withdrawal, decreased play, or participation in usual activities. Prolonged, persistent, or chronic fatigue may be observed in a wide variety of childhood illnesses, including infectious, inflammatory, and malignant processes. In addition, severe stress, anxiety, depression, and dysfunctional family dynamics may be among some of the psychiatric conditions that may produce chronic fatigue. Some medications, including chemotherapy regimens used for the treatment of cancer, can cause fatigue and generalized weakness. Fatigue is also a common complaint among patients with chronic, progressive disease, particularly when dyspnea, pain, or other significant symptoms are present and unrelieved for a period of time.

Except for a symptom assessment tool described by Collins (9), there are no other reliable tools to measure fatigue in children and, as in other age groups, verbal report should constitute the basis for intervention. It is important to exclude common causes of prolonged fatigue such as anemia, hypothyroidism, sleep disturbances, anxiety, and depression, among others. A good history and physical examination may point to other potential causes that may respond to therapy. If available, treatment should be directed at the medical or psychiatric condition most likely associated with fatigue. In addition, a graded and gradual increase in exercise and rehabilitation may be helpful. Cognitive-behavioral approaches may also be an effective counseling technique to assist the child in switching to a more adaptive coping strategy. Whenever possible, graded reintegration with peer and school activities is recommended. The use of drugs has not been explored well in children. Steroids, transfusion of blood products, thyroxine, recombinant erythropoietin, and methylphenidate have been used in the treatment of fatigue with varying results.

Neurological Symptoms

Some of the more common and distressing neurological symptoms in children with malignant disease may include seizures, headaches, and sleep disturbances. Children with neurodegenerative disorders or static encephalopathies may suffer from muscle weakness, muscle spasms, contractures, progressive immobility, and loss or nongain of developmental milestones and communication difficulties. An interdisciplinary approach to these complex symptoms often requires not only the palliative care team but also rehabilitation specialists, neurologists, speech therapists, occupational and physical therapists, and equipment specialists, for example. A proactive, preventive approach, coupled with patient-family education, is paramount.

Seizures in children with malignancy are often due to primary or metastatic brain lesions, metabolic disturbances, or as a side effect of chemoradiotherapy or medications. For children with known seizures, maintenance medications are appropriate; for children at risk for seizures, availability of at least one anticonvulsant in the home should be planned. For children unable to take medications orally, as most would be during a generalized seizure, administration of several agents by alternative routes is possible, including valproic acid, phenytoin, pentobarbital, lorazepam, and diazepam rectally, lorazepam sublingually, midazolam and phenobarbital subcutaneously, and fosphenytoin, phenobarbital, and lorazepam intramuscularly. Rectal diazepam gel provides premeasured medication in a convenient dose delivery device; its efficacy and safety in childhood have been demonstrated in randomized clinical trials (70).

Headache, like seizures, is often multifactorial. A careful history and examination of the child will often suggest the cause. Increased intracranial pressure may result in symptoms associated with headache, such as nausea, vomiting, photophobia, lethargy, transient neurological deficits, or severe irritability, in the preverbal child. Depending on the cause, increased intracranial pressure may be treated with surgery, chemotherapy, radiotherapy, steroids, or expectant management only. Immediate and aggressive use of analgesics, antiemetics, and, often, benzodiazepines, is critical for management of rapidly escalating headache.

For children oversedated from opiates, the addition of adjuvant medications may permit dose reductions. The use of long-acting oral preparations or continuous parenteral infusions may reduce periods of increased sedation due to large bolus doses. The consideration of locally directed therapies for local and regional pain syndromes, and/or addition of psychostimulants such as methylphenidate or dexamphetamine in the morning and at lunchtime (starting at 0.1 mg/kg/dose, maximum 0.5 mg/kg/dose), can significantly improve quality of life.

Sleep disturbance and insomnia in children often are undetected unless specifically elicited in the history. Problem sleeplessness in children may result from behavioral, circadian, biological, or medical abnormalities (71). Sleep problems of varied nature and intensity are more common among young, school-age children but decrease significantly over the primary school years (72). In chronically ill children, the presence of other symptoms, such as pain, dyspnea, or wheezing, and emotional symptoms, such as anxiety, may be contributing factors and should be treated aggressively. Hypnotics are the mainstay for therapy for inadequate sleep; low-dose tricyclic antidepressants, such as amitriptyline, may also be appropriate, particularly for children also presenting with neuropathic pain.

PSYCHOSOCIAL SUPPORT

The death of a child is the most catastrophic loss a human being can face, and is inherently difficult to prepare for. Life-threatening pediatric illness is a major stressor that precipitates the development of emotional and spiritual distress in children, caregivers, and the broader community to which the child belongs. Psychosocial support in palliative care calls for attention to effective communication and informed decision making to assure optimum quality of life and to decrease suffering in all of its dimensions. Good psychosocial care encompasses listening empathically and asking questions, providing honest information, talking about feelings and fears, and identifying hopes and realistic goals of care. Hopes for peaceful death, comfort, lack of suffering, and nonabandonment and escalating engagement with the health care team and community should be stressed.

Children are part of an integrated system formed by many components, including parents, siblings, relatives, caregivers, and the broader community, including religious, educational, and recreational connections. Psychosocial support of the child and family includes addressing the needs of all communities involved in the life of the sick child. Palliative care teams must include services to provide care and support for the siblings of seriously ill children, and extend their educational activities to school classmates and religious programs involved in the life of the sick child (73).

There are consistent themes that prevail across most families. Sick children and their parents need to feel in control of some aspects of their lives. Maintaining a sense of normalcy in the child's life is equally important. Many of the challenges that patients and families must deal with become overwhelming in the face of uncertainty. Children and their parents generally want to understand their illness, know what to expect, and discuss strategies for treatment and comfort. Central to the existence of the dying person, adult and child alike, are the needs to have meaningful relationships, a sense of completion in one's life, a sense of meaning, and a sense of unconditional love. In addition, surviving family members experience significant emotional and spiritual morbidity after the death of the child and the need to provide support during the bereavement process can never be overemphasized (74).

The beliefs, attitudes, and functional dynamics of individual family members, the family unit, as well as of the extended community, have a significant influence on the child's experience of severe disease and death (75). Families with low cohesion, high conflict, and poor conflict resolution report higher intensity of grief and psychosocial morbidity (76). In parents of children diagnosed with cancer, high levels of emotional distress correlate with marital tension, feelings of isolation, and the need for more counseling for themselves (77). Palliative care teams and psychosocial providers must assess patients and families and identify whether these and other needs are being fulfilled.

Table 76-7 describes the illness experience according to the child's stage of cognitive development. The psychological adaptation of the primary caregivers to the challenges of serious illness is important for the mental health of the children (78,79 and 80). Interventions to assist children and their caregivers in developing adequate coping skills to avoid inappropriate and destructive behaviors, and provide individual, couple, family, child, and adolescent counseling are important and

should be recommended. One must keep in mind, however, that the impending death of a child may not necessarily alter a family's coping style—the team must first seek to understand the family. Members of the interdisciplinary team help patients and families to recognize the factors that contribute to their experience of suffering, and support them in their quest to fulfill the universal needs of meaning, purpose, value, self-worth, and a sense of competence in the care of their child (81). The team must also help patients and families with the “letting go” process of anticipatory grieving, and assist them in developing and maintaining adequate coping mechanisms which correlate with bereavement outcomes after the death of the child (82). In a series of intensive care patients, for example, mothers who receive support designed to increased their coping skills provided more support to their children and reported less negative mood state and parental stress (83). Psychosocial interventions in palliative care can also be directed to encourage honest communication between children, their families, and health care professionals, and strengthen interpersonal relationships so that they may feel connected and part of each other. The palliative care team can gently encourage the patient and the family to act on the opportunities for reconciliation, to express their love for each other, their forgiveness of past transgressions, and their gratitude. Interventions also aim to help patients understand their condition, to participate in the decisionmaking process, and to restore their sense of personal integrity, dignity, autonomy, self-mastery, and self-control.

TABLE 76-7. ILLNESS EXPERIENCE

Family support and family therapy are important means of intervention for seriously ill children and their families to improve family function, particularly cohesiveness, conflict resolution, and expression of thoughts and feelings (84). A group experience with other chronically ill children provides an opportunity to observe others with similar problems and attenuates feelings of being singled out. This support group creates opportunities for social interaction, constructive peer relationships, and serves as an outlet for active verbal and social expressions. Group treatment methods with the chronically ill child can mobilize the development potential of group relationships to master special adversity and foster growth (85). Patients and individual family members identified as having high levels of anxiety or clinical depression can be referred for individual counseling or psychiatric evaluation and possible pharmacotherapy by a child psychiatrist and member of the palliative care team.

Children's Understanding of Death

Most children suffering from a life-limiting illness understand death better than other children their age. Their learning is primarily determined by their personal experiences with disease, the death of their peers and important adults in their lives, and their stage of emotional and cognitive development. From birth to 3 years, children grasp events at the level of feeling and action which corresponds to Piaget's sensorimotor stage of cognitive development. Children at this age may interpret death as a temporary separation or abandonment. During Piaget's preoperational stage of cognitive development, children ages 3–6 years view death as a state of immobility which may be temporary and reversible. Between 6 and 12 years of age, during Piaget's stage of concrete operations, children begin to realize that people who die are not able to function. By the age of 7, most children recognize the four major concepts regarding death: irreversibility, finality, inevitability, and causality (86). As children enter Piaget's stage of formal operations, which usually spans from 12 years of age onward, they develop the ability for abstract reasoning, and their thoughts about death are similar to those of a mature adult. It is again important to note that chronically ill and dying children, given the appropriate explanations, may come to understand concepts of death and dying well beyond that expected for their chronological age.

It is also important to talk to children about their illness with openness and honesty. Keeping information from a child is not only futile but also harmful. One must be careful, however, not to strip away the child's resources used to cope with severe illness, at times manifested as avoidant behavior (87). Children cannot envision their own death easily. They think only old people die and cannot understand why. It is not until the later stages of cognitive development when children are able to foresee death as an ever-present possibility in their own lives. It is often helpful to let children guide the conversations about difficult issues. Caregivers can guide those conversations by creating the opportunities for the child to express his or her emotions, which are often varied and complex. Stories, games, play, art, or music are among many tools that caregivers have to stimulate communication by helping children to freely express their thoughts and emotions.

Adjustment Disorder

Chronically ill children who have difficulty coping with the challenges imposed on their lives are often diagnosed as having an adjustment disorder. The essential feature of an adjustment disorder is the development of clinically significant emotional or behavioral symptoms in response to identifiable psychosocial stressors. This must be distinguished from the nonpathological reactions to stress. The definition of adjustment disorder implies that caregivers must make a determination of whether the patient is experiencing distress in excess of what would be expected given the nature of the illness and whether there is significant impairment in the child's age-appropriate social and cognitive functioning. This assessment may be particularly difficult in the severely ill child who often experiences multiple medical problems and who may be at the end of his or her life. Children with serious and chronic illness are at increased risk for adjustment disorders (88). When present, these may occur with depressed mood, anxiety, disturbance of conduct, or a combination of these. Identification of children who may have difficulty adjusting is important as most of these children may benefit from appropriate behavioral and cognitive-behavioral therapies.

Anxiety

Anxiety disorders are one of the most prevalent categories of childhood and adolescent psychopathology (89). The assessment and treatment of anxiety disorders in childhood and adolescents is well studied, and excellent reviews of the subject are available (90). One of the dilemmas in clinical practice is to define what constitutes an anxiety disorder in comparison with normal anxiety in the presence of stressful life circumstances. Separation anxiety, generalized anxiety disorder, and social phobia are among the most prevalent anxiety disorders in children. Adolescents also begin to develop vulnerability to other anxiety disorders, including panic disorder and agoraphobia. Anxiety disorders in children often do not appear in isolation but as part of a broad array of other symptoms and maladaptive traits such as timidity, social withdrawal from novel or unfamiliar situations, lack of selfconfidence, dysphoria, and hypersensitivity among others.

Seriously ill children are under considerable personal and family strain and may experience symptoms of anxiety as a manifestation of psychological distress without meeting the criteria for diagnosis of an anxiety disorder. Children who experience difficulty functioning as a result of their anxiety symptoms may have an adaptive disorder. Some of the most common subclinical anxiety symptoms in children include overconcern about competence, excessive need for reassurance, fear of the dark, fear of harm to self or an attachment figure, and somatic complaints. In addition to the stress inherent to serious disease, other sources of anxiety for adolescents include consolidation of identity, sexuality, social acceptance, and independence conflicts. Teenagers may also manifest unrealistic fears, excessive worry about past behavior, and self-consciousness as signs of increased anxiety.

The presence of traumatic events in the child's life and limited access to support systems may account for the development of anxiety in children. About half of all mothers and fathers of children with cancer report high levels of distress (91). At least one-third of the children with anxiety disorders have other comorbid anxiety disorders, major depression, or attention-deficit hyperactivity disorder. Anxiety also affects school performance in children. Family history is essential as the rate of anxiety disorders is higher in children of adults with anxiety disorders.

Anxious children generally benefit from mastering themes of separation, autonomy, self-esteem, and ageappropriate behavior. Parents should be involved in the treatment so they learn to understand the patient's need for reassurance and to encourage the child to be more independent. Parents may need to resolve their own issues about separation and other sources of anxiety because they may exacerbate fears or communicate ambivalence about their child's safety, security, and autonomy (92). Working with the family system is the key way to decrease the anxiety symptoms experienced by the child. The aim of the therapy is to disrupt the dysfunctional patterns of interaction that promote family insecurity and to support areas of family competence. Attention to the child-parent relationship is vital for preventing and treating anxiety symptoms. Behavioral therapy, cognitive-behavioral therapy, and psychodynamic psychotherapy are useful therapeutic techniques to help the child and family in the process of coping with the challenges of a life-limiting illness.

Pharmacological treatment should not be used as the sole intervention but as an adjunct to behavioral and psychotherapeutic interventions. Commonly selected

medications for treating anxiety symptoms include tricyclic antidepressants and selective serotonin reuptake inhibitors. Selection of the medication depends on the presence of comorbidity. Tricyclic antidepressants may be used in the treatment of anxiety if enuresis is also present. Selective serotonin reuptake inhibitors may be used if there is an associated obsessive-compulsive disorder or depression. Either of these therapeutic avenues may also be appropriate for children with neuropathic pain or disturbed sleep. Benzodiazepines may be used on a short-term basis for anxiety symptoms.

Depression

Major depression and dysthymia are common disorders occurring in children and adolescents. Guidelines for the assessment and treatment of children and adolescents with depressive disorders are available (93,94 and 95). Fortunately, while children with medical problems appear to be at slightly elevated risk for depression and have higher rates of maladjustment, the majority of children with chronic disease are not depressed. In a series of children with cancer, for example, patients had unexpectedly low levels of depression, which can be attributed to a defensive bias as a mechanism to minimize the experience of distress (96). Whether clinical depression is more prevalent in terminally ill children as compared with other chronically ill children or healthy controls is not known.

Depressive disorders affect a child's development of social, emotional, cognitive, and interpersonal skills and the attachment between parent and child. The clinical picture of depression in children and adolescents varies considerably across different developmental stages. Younger children may show more somatic complaints, auditory hallucinations, temper tantrums, and other behavioral problems. Older children may report low self-esteem, guilt, and hopelessness. The family relationships of youth with depressive symptomatology frequently are characterized by conflict, maltreatment, rejection, and problems with communication, with little expression of positive affect and support. Parents of these children may themselves be depressed or have other illnesses that may interfere with their effectiveness in parenting. Every child can be sad occasionally. For children at the end of life, depressive symptoms may occur as a normal reaction to grief and could suggest the need to explore their fears and concerns, and find support in their search for meaning and understanding of their disease, suffering, and imminent death.

The most important tool in diagnosis of depression in children is the comprehensive psychiatric evaluation that should be conducted by a trained clinician. Standardized interviews are too long for use in clinical settings. In addition, some of these tests may not be appropriate for children with chronic illness in whom “depressive” symptoms, such as sleep, fatigue, or decreased performance, may be related to the illness without representing depression. Psychiatric symptom checklists derived from these standardized interviews have been developed and can be useful screening tools. Examining the role of factors associated with depression of children without a chronic illness, such as life stress, family functioning, and attributional style, as well as stressors unique to their medical condition and end-of-life situation, may assist clinicians in planning interventions (97).

The treatment of depressive youth should be provided in the least restrictive treatment setting that is safe and effective for a given patient. Given the developmental and psychosocial context in which depression unfolds, pharmacotherapy alone usually is not sufficient. Treatment may include a combination of cognitive-behavioral therapy, interpersonal therapy, psychodynamic psychotherapy, and other psychotherapies. For patients requiring pharmacotherapy, selective serotonin reuptake inhibitors are the initial treatment of choice.

SPIRITUAL SUPPORT

Patients and their families are especially concerned with spirituality in the contexts of suffering, debilitation, and dying (98). Spirituality is that part of our human nature that enables us to find a sense of meaning in our experiences. Many agree that the key to emotional coping with serious illness and disability is frequently found within the matrix of spirituality (99). Spirituality gives us meaning and direction, and brings a sense of order into our lives. This is equally true for children. Children, as well as adults, ask questions, search for a deeper understanding of their experiences, and express their emotions in response to their own interpretation of reality (100).

Seriously ill patients live deeply spiritual lives. Children, however, are likely to base their spirituality on the relationship with their parents or other primary caregivers. Children's spirituality matures and evolves out of these important relationships, which suggests that spiritual care should be offered to the patient as well as his or her family. In addition, children often take religious teachings literally and require explanations beyond these literal meanings to assist them in the process of understanding and interpreting their life experiences. Moreover, children may experience existential suffering, which can be intense during this process and manifested as a lack of order and meaning in their lives and a sense of abandonment.

Tools that can assist in the assessment of spiritual needs in children and their families can be found in the Compendium of Pediatric Palliative Care (19) published by the National Hospice and Palliative Care Organization. Assessment of the family dynamics is important. Some families have informal rules that interfere with the child's ability to express emotions and ask questions about the illness and possible death. The lack of guidance may lead children to experience guilt and self-blame. The developmental stages may assist in the determination of appropriate interventions for spiritual care for the seriously ill child. Typically, these interventions emphasize continued engagement with the child and caregivers, including thoughtful, age-appropriate questioning. Spiritual interventions introduced into the mainstream of medical therapy are directed to help children articulate their questions, express their emotions, and search for creative answers. These activities may allow patients and their families to discover meaning and purpose in their experiences, a sense of oneness with life, of belonging to something beyond themselves, of being part of something greater. This spiritual experience of transcendence beyond the self may facilitate coping by providing a sense of order despite the experience of serious illness and death. Many times at this stage, patients and families manifest a deep yearning for life but also a willingness to accept death, and to live their lives in harmony, giving and receiving love. Suggested spiritual interventions are included in Table 76-7.

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GERIATRIC PALLIATIVE CARE

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In our society, the overwhelming majority of people who die are elderly. They typically die slowly of chronic diseases, over long periods of time, with multiple coexisting problems, progressive dependency on others, and heavy care needs met mostly by family members. They spend the majority of their final months and years at home but, in most parts of the country, actually die surrounded by strangers in the hospital or nursing home. Abundant evidence suggests that the quality of life during the dying process is often poor, characterized by inadequately treated physical distress, fragmented care systems, poor to absent communication between doctors and patients and families, and enormous strains on family caregiver and support systems. In this chapter, we focus on the palliative care needs of older adults.

BIOLOGY OF AGING

Body Composition

Aging is a process that converts healthy adults into frail ones with diminished reserves in most physiologic systems and with an exponentially increasing vulnerability to most diseases and death (1). Aging is the most significant and common risk factor for disease in general. The process itself is a mystery, still poorly understood even in this age of advanced biotechnologic capability. Normal aging appears to be a fairly benign process. The body's organ system reserves and homeostatic control mechanisms steadily decline. Commonly, this slow erosion only becomes obvious in times of maximum body stress or serious illness. However, as the process continues, it takes less and less insult for the underlying physiologic weakness to become apparent. It is difficult to differentiate the effects of aging alone from those of concurrent disease or environmental factors. Eventually, a critical point is reached, when the body's systems are overwhelmed, and death ultimately results. Morbidity is often compressed into the last period of life (2).

Substantial changes occur in body composition with aging. These changes become important when related to nutritional needs, pharmacokinetics, and metabolic activity. As adults age, the proportion of bodily lipid doubles and lean body mass decreases. Bones and viscera shrink and the basal metabolic rate declines. Although specific age-associated changes occur in each organ system, changes in body composition and metabolism are highly variable from individual to individual.

Renal Function

The aging kidney loses functioning nephrons. Cross-sectional and longitudinal studies have also demonstrated a decline in creatinine clearance. There is also evidence to show decreased renal plasma flow, decreased tubular secretion and reabsorption, decreased hydrogen secretion and decreased water absorption and excretion (3). When kidney disease complicates this aging process, the outcome can be highly deleterious.

Underlying renal function is an important issue in geriatric pharmacology. Many medications rely on the kidneys' mechanisms for excretion and their metabolites may accumulate and lead to side effects or toxic injury in an impaired system. For example, the renally cleared metabolite meperidine, normeperidine, can accumulate in the elderly and predispose to delirium, central nervous system excitement, and seizure activity. Commonly used medications are more likely to damage older kidneys, including nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, and intravenous contrast dye (4).

Gastrointestinal and Hepatic Function

The gastrointestinal tract changes less with aging than normal systems, but there are still some deficiencies that may affect medication delivery and breakdown, as well as nutritional status and metabolism. The esophagus may show delayed transit time. The stomach may atrophy and produce less acid. Colonic transit is greatly slowed, while small intestinal transit appears unaffected. Pancreatic function is usually well maintained, although trypsin secretion may be decreased.

The liver usually retains adequate function, although there are variable changes seen in its metabolic pathways. The cytochrome P-450 system may decline in efficiency and liver enzymes may be less inducible. The most significant change is the sharp decline in demethylization, the process that metabolizes medications such as benzodiazepines in the liver. This change may necessitate dosage adjustments. In addition, drugs that undergo hepatic first pass metabolism by extraction from the blood may have altered clearance with increasing age due to decreased hepatic blood flow.

Brain and Central Nervous System Changes

The brain and central nervous system slowly atrophy with age. Neurons stop proliferating and are not replaced when they die, resulting in neuronal loss as well as loss of dendritic arborization. These are also some degree of neurotransmitter and receptor loss. The extent of this loss is not well understood.

Age-related changes in pain perception may exist, but their clinical importance is uncertain. Although degenerative changes occur in areas of the central and autonomic nervous system that mediate pain, the relevance of these changes has yet to be determined (5). Clinical observations from elderly patients who report minimal pain and discomfort despite the presence of cardiac ischemia or intraabdominal catastrophe suggest that pain perception may be altered in the elderly. However, experimental data suggest that significant, age-related changes in pain perception probably do not occur (6). Until further studies conclusively demonstrate that the perception of pain decreases with age, stereotyping of most elderly patients as experiencing less pain may lead to inaccurate clinical assessments and needless suffering (5).

DEMOGRAPHY OF DYING AND DEATH IN THE UNITED STATES

The median age at death in the United States is now 77 years and has been associated with a steady and linear decline in age-adjusted death rates since 1940. In 1900, life expectancy at birth was less than 50 years; a girl born today may expect to live to age 79 and a boy to age 73. Those reaching 65 years can expect to live another 18 years on average and those reaching age 80 can expect to live an additional 8 years. These unprecedented increases in life expectancy (equivalent to that occurring between the Stone Age and 1900) are due primarily to decreases in maternal and infant mortality, resulting from improved sanitation, nutrition, and effective control of infectious diseases. As a result, there has been an enormous growth in the number and health of the elderly. By the year 2030, 20% of the United States' population will be over age 65, as compared to fewer than 5% at the turn of the twentieth century (7).

Although death at the turn of the twentieth century was largely attributable to acute infectious diseases or accidents, the leading causes of death today are chronic illness such as heart disease, cancer, stroke, and dementia. With advances in the treatment of atherosclerotic vascular disease and cancer, many patients with these diseases now survive for years. Many diseases that were rapidly fatal in the past have now become chronic illnesses.

In parallel, deaths that occurred at home in the early part of the twentieth century now occur primarily in institutions (57% in hospitals and 17% in nursing homes) (8). The reasons for this shift in location of death are complex, but appear to be related to health system and reimbursement structures that promote hospital-based care and provide relatively little support for home care and custodial care services despite the significant care burdens and functional dependency that accompany life-threatening chronic disease in the elderly. The older the patient, the higher the likelihood of death in a nursing home or hospital, with an estimated 58% of persons

over 85 spending at least some time in a nursing home during the last year of their life (8). These statistics, however, hide the fact that the majority of an older person's last months and years is still spent at home in the care of family members, with hospitalization and/or nursing home placement occurring only near the very end of life. National statistics also obscure the variability in the experience of dying. For example, the need for institutionalization or paid formal caregivers in the last months of life is much higher among the poor and women. Similarly, persons suffering from cognitive impairment and dementia are much more likely to spend their last days in a nursing home compared with cognitively intact, elderly persons dying from nondementing illnesses.

CARE SYSTEMS FOR OLDER ADULTS WITH SERIOUS AND LIFE-THREATENING ILLNESS

The incentives promoting an institutional—as opposed to home—death persist despite evidence that patients prefer to die at home. These incentives persist in the United States despite the existence of the Medicare Hospice Benefit (9), which was designed to provide substantial professional and material support (medications, equipment, skilled nursing visits) to families caring for the dying at home for their last 6 months of life. Reasons for the low rate of utilization of the Medicare Hospice Benefit vary by community but include the inhibiting requirements that patients acknowledge that they are dying in order to access the services, that physicians certify a prognosis of 6 months or less, and that very few hours (usually 4 or less) of personal care home attendants are covered under the benefit. In addition, the fiscal structure of the Medicare Hospice Benefit lends itself well to the predictable trajectory of late-stage cancers or AIDS, but not so well to the unpredictable chronic course of other common causes of death in the elderly such as congestive heart failure, chronic lung disease, stroke, and dementing illnesses.

Traditional Medicare coverage in the United States also fails to meet the needs of the seriously ill, older adult. Neither paid personal care services at home nor nursing home costs for the functionally dependent elderly are covered by Medicare, but instead are paid for approximately equally from out-of-pocket and Medicaid budgetary sources that were originally developed to provide care for the indigent.

In nursing homes, standards of care focus on improvement of function, and maintenance of weight and nutritional status. Evidence of the decline that accompanies the dying process is typically regarded as a measure of substandard care (10). Thus, a death in a nursing home is often viewed as evidence, particularly by state regulators, of poor care rather than an expected outcome for a frail, chronically ill, older person. The financial and regulatory incentives and quality measures that currently exist in long-term care promote tube feeding over spoon feeding and transfer to hospital or emergency department in the setting of acute illness or impending death. They fail to either assess or reward appropriate attention to palliative measures, including relief of symptoms, spiritual care, and promotion of continuity with concomitant avoidance of brink-of-death emergency room and hospital transfers (11).

PALLIATIVE CARE NEEDS OF OLDER ADULTS

Although death occurs far more commonly in older adults than in any other age group, remarkably little is known about how death occurs in the oldest old, those over age 75. Most research on the experience of dying has been done in younger populations, and most studies examining pain and symptom management have focused on younger populations with cancer or AIDS. Studies in older adults have focused primarily on patients' preferences for care rather than the actual care received. Indeed, the largest study to date of the dying experience in the United States (SUPPORT) studied the hospital experience of patients with a median age of 66 years (9). The median age of death in the United States is 77 years, and many of the oldest old die in nursing homes or at home rather than in hospital. Data from Medicare and state Medicaid registries suggest that expensive and high technology interventions are less frequently applied to the oldest patients, independent of functional status and projected life expectancy. Whereas these discrepancies may reflect patient preferences and indicate appropriate utilization of resources and patient preferences, it is more likely that they represent a form of implicit rationing of resources based on age. The implication is disturbing, considering that half of the highest-cost, Medicare enrollees survive at least 1 year (12).

Aside from pain and other sources of physical distress (discussed below [see the section Symptom Management: The Challenge of Pain]), the key characteristic that distinguishes the dying process in the elderly from that experienced by younger groups is the nearly universal occurrence of long periods of functional dependency and need for family caregivers in the last months to years of life. In SUPPORT, the median age of participants was 66 years and 55% of patients had persistent and serious family caregiving needs during the course of their terminal illness (13), and in another study of 988 terminally ill patients, 35% of families had substantial care needs (14). This percentage rises exponentially with increasing age. Although paid care supplements or provides the sole source of care in 15–20% of patients (transportation, homemaker services, personal care, and more skilled nursing care), the remaining 80–85% of patients receive the majority of their care from unpaid family members (14). Furthermore, most family caregiving is provided by women (spouses and adult daughters and daughters-in-law), placing significant strains on the physical, emotional, and socioeconomic status of the caregivers. Those ill and dependent patients without family caregivers, or those whose caregivers can no longer provide nor afford needed services, are placed in nursing homes. In the United States, this typically occurs after patients exhaust all of their financial savings in order to become eligible for Medicaid. At present, 20% of the over age 85 population reside in a skilled nursing facility, and this number is expected to increase dramatically in the next 50 years (15). Present estimates suggest the current number of skilled nursing facility beds in the United States will be woefully inadequate for the needs of our aging population.

SYMPTOM MANAGEMENT: THE CHALLENGE OF PAIN

The constellation of symptoms seen in dying, older, adult patients is different from that of young adults. Delirium, sensory impairment, incontinence, dizziness, cough, and constipation are more prevalent in older adults (16). The elderly, on average, have 1.5 more symptoms than younger persons in the year prior to death, and 69% of the symptoms reported for people aged 85 or more lasted more than a year as compared with 39% of those for younger adults (less than 55 years) (16).

Studies focusing specifically on the prevalence of pain have shown consistently high levels of untreated or undertreated pain in older adults. In one study of elderly cancer patients in nursing homes, 26% of patients with daily pain received no analgesic at all and 16% received only acetaminophen, a percentage that rose with increasing age and minority status (17). A subsequent study revealed that 41% of patients who were assessed to have pain on their first assessment continued to have moderate or excruciating daily pain on their second assessment 60–180 days later (18). Studies comparing pain management in cognitively intact versus demented elderly with acute hip fracture also found a high rate of undertreatment of pain in both groups, a phenomenon that worsened with increasing age and cognitive impairment (19,20). Similarly, a study of outpatients with cancer found that age and female sex were predictors of undertreatment, a disturbing observation given the dramatic rise in cancer prevalence with increasing age (21,22). Chronic pain due to arthritis, other bone and joint disorders, and low back pain syndrome is probably the most common cause of distress and disability in the elderly, affecting 25–50% of community-dwelling, older adults. It is likely that these symptoms also are consistently undertreated (23). These data suggest that the time before death among elderly persons is often characterized by significant physical distress that is neither identified nor properly treated.

Despite the high prevalence of pain and other symptoms in the elderly, most studies focusing on the assessment and treatment of pain and other symptoms have enrolled young cancer patients. It is unclear whether these results are generalizable to a geriatric population. Pain assessment in the elderly is often complicated by the coexistence of cognitive impairment. The assessment and management of pain in the cognitively impaired patient present special challenges to the health care professional. The cognitively impaired patient is often unable to express pain adequately, request analgesics, or operate patient-controlled, analgesia devices. This increases the risk of undertreatment. The fear of precipitating or exacerbating a delirious episode by employing opioids in the management of pain may also lead to inadequate pain management.

As with the cognitively intact patient, the initial step in the assessment of pain in the demented individual is to ask the patient. Although patients with severe dementia may be incapable of communicating, many patients with moderate degrees of impairment can accurately localize and grade the severity of their pain (24,25). In the noncommunicative patient, alternative means of assessment must be identified. The need for careful pain assessment in this population of patients is underscored by evidence that suggests that medical professionals undertreat pain in the presence of cognitive impairment (19,20,26) and that pain may be aggravated in the presence of cognitive deficits (24). Untreated pain can result in agitation, disruptive behavior, and may worsen or precipitate a delirious episode (27,28 and 29).

Pain assessment in the noncommunicative patient should begin with observation of both nonverbal cues, such as facial expressions (grimacing, frowning) and motor behavior (bracing, restlessness, agitation), and verbal cues, such as groaning, screaming, or moaning. Data from cognitively intact individuals suggest that nonverbal behaviors correlate with self-reported pain in nondemented patients recovering from surgery (30,31). Pharmacological therapy should be titrated upwards in small, incremental doses until the nonverbal/verbal behavior disappears or side effects become apparent. This approach is particularly useful in the agitated patient whose behavior may well stem from untreated or undertreated pain. The risk of undertreating severe pain is generally more concerning, both medically and ethically, than the risk of worsening delirium with medications.

Pharmacological therapy for pain must be modified in older adults. The World Health Organization's analgesic ladder approach may not be appropriate for the elderly. For example, the increased risk of side effects, including renal failure and gastrointestinal bleeding, mandates great caution in the use of NSAIDs. This caution extends to currently available parenteral NSAIDs because of the significantly increased risk of gastrointestinal bleeding, particularly with higher doses and with duration of use greater than 5 days (32,33 and 34). Selective COX-2 antagonists have been associated with a decreased incidence of gastrointestinal events and are probably preferred for use in older adults over traditional NSAIDs (35,36 and 37). A recent systematic review, however, suggest that there may be an increase in adverse cardiovascular events associated with the use of COX-2 inhibitors although the magnitude of this risk has yet to be determined (38). The American Geriatrics Society has recently recommended that opioids be considered as a first step treatment rather than NSAIDs (23). If NSAIDs are used, careful monitoring of renal function and

close observation for the development of gastrointestinal bleeding must be undertaken.

Opioid therapy remains the cornerstone of pain management in palliative care and this is also true for older adults. Some aspects of opioid therapy require special consideration in the elderly. Older adults will have a more pronounced pharmacological effect after any weight-adjusted opioid dose than younger patients. The analgesia is more intense, and cognitive and respiratory effects, and perhaps constipation, are more severe. This enhanced effect is likely due to a lesser volume of distribution (approximately half that of younger patients), a decreased clearance, and diminished target organ reserve (central nervous system, pulmonary function, and bowel function). Age is the single most important predictor of initial opioid dose requirements for postoperative pain (39). The following formula, based on a review of records of more than 1000 adults between age 20 and 70 years undergoing major surgery, provides a rough estimate of the appropriate starting dose in parenteral morphine sulfate equivalents for adult opioid naive patients (with the exception of the old-old): average first 24-hour morphine (mg) requirement for patients over 20 years of age = 100 – age (39). Other factors that will influence opioid effects, but to a lesser degree than that of age, are body weight, severity of pain, abnormal renal function, nausea/vomiting, and cardiopulmonary insufficiency. After the initial dose determination, drugs should be titrated based on analgesic effect.

Several opioids are best avoided in older adults. Meperidine is particularly hazardous as a result of the accumulation of its toxic metabolite, normeperidine, in patients with impaired renal function. Indeed, toxic levels can accumulate in older adults with “normal kidneys” due to age-related changes in creatinine clearance. There are almost no circumstances in which meperidine should be used on older adults. Similarly, pentazocine should also be avoided in older adults because of the increased incidence of delirium and agitation associated with its use. Finally, opioids with long half-lives (e.g., methadone, levorphanol) or opioids with sustained release preparations (e.g., sustained release morphine and oxycodone, and transdermal fentanyl) should be used with caution, rarely used in opioid naïve geriatric patients, and should probably only be used following steady state accumulation of shorter acting opioids.

With respect to adjuvant agents, amitriptyline and the other tricyclic antidepressants, although efficacious in some neuropathic pain syndromes, are poorly tolerated in older adults due to their anticholinergic properties. Bowel and bladder dysfunction, orthostatic hypotension resulting in falls, delirium, movement disorders, and dry mouth are very common with these medications. If tricyclics are to be used, then nortriptyline or desipramine are the agents of choice and initial dosages should be very low and dose titration should be undertaken very slowly.

ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Irreversible dementia is a frightening and difficult diagnosis for geriatric patients and their families. A diagnosis of dementia means a certain and progressive decline in cognitive abilities over time and an eventual loss of independence. The prevalence of dementia increases with each decade of life over age 65. By the age of 80, about 19% of the older adult population will suffer with dementia. Over 80, the prevalence increases to almost 50% and continues to rise with age. Sixty percent of adults older than 100 years carry a diagnosis of dementia (40). Alzheimer's disease is the most common dementia, accounting for 50% of all cases (40). Alzheimer's disease affects over 4 million Americans, and 22 million people worldwide. Vascular dementia is the second most diagnosed type in the United States and accounts for 20–40% of cases. Lewy body disease, Pick's disease, and Creutzfeldt-Jakob disease are less common. Many patients present with a “mixed” picture and may be difficult to categorize clinically (40).

Dementia is a progressive, incurable illness, and all treatments are palliative. The average survival after a diagnosis of Alzheimer's disease ranges from 7–10 years. During this time, persons with dementia pass through different and predictable stages of disease. In the early stages, they may experience mild deficits in memory, judgment, and spatial relationships. They may face difficulties with word finding, driving, or learning new skills. As patients move into the moderate stages of the disease, they lose the ability to perform the instrumental activities of daily living. They may no longer be able to balance their own checkbook or shop for food. Family members or hired home attendants begin to play a larger role in the patient's care. Patients may develop behavioral disturbances, such as agitation, paranoia, or wandering. Advanced dementia patients depend entirely on their caregivers for even the simplest activities of daily living, like dressing, bathing, toileting, and ambulation. They develop a decreased ability to chew and swallow. They may not be able to recognize and remember their caregivers and loved ones. They are unable to describe pain or discomfort and may be nonverbal. Often, they are bedbound. A large proportion eventually require nursing home care.

Patients with dementia require medical care that focuses on preserving dignity and quality of life. Physicians should seek to manage aggressively the symptoms that endanger these goals. This must be done in early stages of the disease, the more moderate stages, and finally the advanced stages. The needs of patients in each stage are different, but the focus is always to preserve dignity and quality of life.

In early dementia, perhaps the most important job for the physician is to recognize and diagnose the disease and then to educate patients and their families about what they can expect. At this stage, patients can still make decisions for themselves. Physicians should ask patients about their preferences for medical treatments in the later stages of their disease and facilitate these important conversations between their patients and caregivers. Specific discussions about life-prolonging treatments, like artificial nutrition and hydration, should take place. Physicians should ask patients to designate one or more primary decision makers to speak for them in preparation for later stages of disease when they are no longer able to make decisions for themselves. Patients should be encouraged to talk with their designated caregivers and loved ones about their views about advanced medical therapies like feeding tubes, mechanical ventilation, and cardiopulmonary resuscitation (CPR). Although it is important to explore patients' specific preferences with regard to medical technology, it is equally important to explore the patients' values and goals of medical care: What is most important in their lives? What makes their lives worth living? What religious or spiritual values may be important? There is evidence that early conversations about advance directives help to prepare families for future decision making and may reduce the difficulty that comes with later surrogate decision making (41).

The early stages of Alzheimer's disease may be amenable to pharmacological therapy with cholinesterase inhibitors. Treatment with these medications may improve performance in activities of daily living, modestly improve cognitive function, or slow the progression of the disease process. Aggressive control of vascular risk factors and the use of aspirin and cholesterol-lowering agents may slow the progress of vascular dementia. The goals of both types of therapies are to preserve independence for as long as possible.

Many patients with early-stage disease have concurrent psychiatric issues. Depression is especially common, affecting approximately 50% of the early Alzheimer's disease population (42). The symptoms of depression in early disease may be atypical and include indifference, difficulties with emotional engagement, and decreased motivation. Antidepressant therapies are often indicated, and cholinesterase inhibitors may be beneficial. Support groups may also be helpful at this stage of disease, both for patients and their caregivers.

Moderate-stage dementia is the longest stage of the disease. The physician's focus should be keeping the patient's environment safe, treating psychiatric symptoms, and supporting the patient's caregivers. As patients move to this more middle stage of disease, their need for supervision at home and help with performing activities of daily living become greater. Behavioral disturbances, agitation, and paranoia often occur in concert with increased dependence. These changes may become significant sources of caregiver stress. Palliative measures in moderate-level dementia include recognition and attention to caregiver stress, treatment of behavioral and psychiatric disturbance, and instituting environmental safety modifications. Additionally, patients with a moderate degree of cognitive impairment often exhibit impaired eating behaviors, and physicians must work with patients and their caregivers to meet nutritional demands, as well as modifying food products for easier mealtimes.

Caregiver stress is common as relatives take on a more active and demanding role in the everyday routines of patients with progressive dementia. Many have never been in the role of primary caregiver for anyone other than their own children. Some primary caregivers may be geriatric patients themselves. Most families will face a high level of financial stress. Unless a patient has access to social services (Medicaid in the United States), out-of-pocket costs for additional help at home, pharmaceutical products, and durable medical equipment are high. Adult day programs may be hard to find, and respite programs are typically expensive. Patients with this degree of cognitive compromise may be difficult to place in nursing homes because often they do not carry other comorbid diagnoses, and the reimbursement rate for pure custodial care is low. Many caregivers leave their jobs or families behind to care for their loved ones. Some need to take on a second job to keep up with the financial burdens.

Caregivers may feel underappreciated because their loved ones fail to acknowledge how hard they are working or the sacrifices they are making. Eventually, patients fail to be able to even recognize who their caregivers are. These very real stresses need to be recognized, acknowledged, and supported. Physicians should question caregivers about fatigue, social isolation, depression, and physical symptoms. They should remind caregivers to take breaks and encourage other family members to help out. Caregiver support groups may also be helpful.

Behavioral disturbances become more frequent as dementia progresses. Although they may occur at any stage of disease, they are associated with increasing cognitive and functional decline. Symptoms include anxiety, depression, paranoia, delusions, hallucinations, sleep disorders, agitation, and combativeness. The presence of behavioral disturbance, especially paranoia and aggression, can increase the likelihood of nursing home placement. Treatment should be aimed at improving the quality of life of the patient and caregiver and should include both pharmacological and nonpharmacological considerations. Careful attention should be given to alternative causes of behavioral disturbance, like uncontrolled pain, untreated infection, or suboptimal management of concurrent disease. Treatment of underlying medical illness may lead to sustained improvement in both cognitive status and behavior. In addition, the etiology of agitation may be based on basic human needs—hunger, thirst, or the need to change wet or soiled clothing. Identifying the root of the problem may be difficult, as patients with moderate degrees of dementia can't tell their caregivers what exactly is bothering them. Nevertheless, the presence of a new behavioral disturbance should precipitate a medical evaluation and

should not simply be considered a consequence of the underlying dementing illness.

Treating obvious etiologies as well as addressing possible modifications in the patient's care environment can be useful ways to address behavioral disturbances. For example, a careful history may demonstrate that agitated and paranoid behavior occurs at bath time. In this case, perhaps changing the water temperature or moving from a tub to a sponge bath may be less threatening for patients and lead to decreased agitation (43). Evidence suggests that involving patients actively in grooming routines may also decrease agitation. Calm environments, the use of usual routines, favorite pieces of music, and visits from children or pets may all be soothing. Attention to a patient's sleeping patterns is also important. Increasing daytime activities and decreasing daytime napping may help patients sleep better at night.

In addition to these behavioral interventions, low-dose standing or as-needed major tranquilizers, such as haloperidol, risperidone, or olanzapine, may be required to successfully manage behavioral disturbances and prevent hospital admissions. Bedtime dosing with major tranquilizers or with trazodone may help with sleep disturbances. Benzodiazepines may be associated with paradoxical agitation, excessive somnolence, and falls, and should be avoided in most patients.

Eating behaviors also change in patients with moderate dementia. Diminished acuity of taste and smell receptors as well as decreased sensitivity in thirst receptors predispose dementia patients to malnutrition and dehydration. Patients may have difficulty using utensils properly. Extra sweeteners and spices may be helpful, as well as supplying frequent nutritious snacks and beverages. Finger foods are a good option. Specially designed utensils or dishes may make feeding easier. Careful attention to concurrent medications that may decrease appetite is warranted. These may include diuretics, beta-blockers, digoxin, and statins and should be discontinued, if possible.

Advanced dementia is the final stage of this terminal disease. Patients with end-stage dementia are dying. Research has demonstrated a median 6-month survival rate for patients with end-stage dementia, with or without tube feeding, although the range of survival times is wide (44,45,46 and 47). Most patients in this stage of disease are bedbound and nonverbal. Many patients in this stage of disease are placed in a nursing home because of their increasing care demands. Although comfort care and palliation of suffering should be the paramount focus of care, patients with advanced dementia often receive nonpalliative interventions at the end of life, such as tube feedings, CPR, mechanical ventilation, and systemic antibiotics in their final days of life (20,45,48,49).

Surrogate decision making in end-stage disease is inevitable. The process is made easier for all involved if, in the early stages of disease, the aforementioned critical discussions of treatment goals and end-of-life preferences have occurred. Caregivers may face multiple, difficult decisions, including emergency surgery, intubation, feeding tubes, and CPR. Even if the advance wishes were well communicated, it may still be difficult for family members to carry them out. Nonetheless, decisions should always be based on previously expressed wishes (if known) and the best interest of the patient with respect to the potential benefits or burdens of the proposed treatment. Physicians should offer caregivers continued support and offer them regular and repeated reviews of the goals of treatment and the expectations that follow interventions.

Comfort measures and the relief of suffering should be the primary palliative goals. Careful attention to potential sources of discomfort, such as pain and concurrent illness, is important. Pain is very commonly overlooked and undertreated in this population. Analgesic therapy should be empiric and preventive if an underlying source exists or the patient faces potentially uncomfortable procedures such as dressing changes or position changes. Physicians also should recognize that patients with advanced dementia may experience more discomfort from routine procedures, such as vital signs monitoring, phlebotomy, finger sticks, and bladder catheterizations, because they cannot understand what is being done to them and why. Unnecessary procedures should be discontinued. Topical anesthetic preparations may make the necessary procedures more bearable.

CONCLUSION

As a result of the unprecedented improvements in maternal and infant mortality and successes in the control, if not cure, of common chronic diseases, most people who die in the United States are old and frail. Conservative projections suggest that in the next 30 years, we will see a dramatic shift in demographics, with over 20% of the United States population being over age 65 in the year 2030. The elderly die of chronic, progressive illnesses (such as end-stage heart and lung disease, cancer, stroke, and dementia). These diseases have unpredictable clinical courses and prognoses, and current care systems are not well adapted to the trajectory of illness or the clinical needs of this group of patients. In contrast to younger adults, older adults often have unrecognized and untreated symptoms, cognitive impairment, and an extremely high prevalence of functional dependency and associated family caregiver burden. It is clear that our current systems of reimbursement are illequipped to provide primary care with continuity, support for family caregivers, and home care and nursing home services. Because care for a frail, older adult typically includes preventive, life-prolonging rehabilitation and palliative measures in varying proportions and intensity based on the individual patient's needs and preferences, any new models of care will have to be responsive to this range of service requirements. Several “mixed management” models of care have recently been proposed to address the needs of the frail elderly. They include the PACE Demonstration Program (50), a capitated Medicare and Medicaid waiver program, and the *MediCaring* model (51,52), a program targeted at patients with advanced heart and lung disease. But these programs have to date targeted only a small percentage of the growing number of older adults. Future research needs to be targeted at understanding the palliative care needs of older adults, developing medical interventions that address these needs, and developing models and systems of care that will meet the global needs of these patients and their families.

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PALLIATIVE CARE IN HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME

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PALLIATIVE CARE AND HUMAN IMMUNODEFICIENCY VIRUS

Palliative care is multiprofessional, interdisciplinary care to relieve suffering and improve quality of life. Palliative care for the patient with human immunodeficiency virus (HIV) infection seeks to meet the individual's physical, social, psychological, and spiritual expectations and needs with sensitivity to personal values, and cultural and religious beliefs and practices (1). This requires the integration of medical, nursing, psychological, social work, spiritual, physical therapy, and pharmacological expertise (2). Care planning includes the individual, family (as defined by the individual), and caregivers. HIV palliative care is not reserved to a single type of health care setting or agency (1,3).

The challenge in caring for patients with HIV is balancing medical treatments aimed at controlling the disease with palliative care designed to relieve suffering and improve quality of life. Contemporary HIV therapy has led the expectation for continued improvements in the ability to provide life-prolonging care (4). At the same time, contemporary therapy does not benefit all patients. “Successful” antiviral therapy can lead to prolonged suffering due to the adverse effects of the medications. Some patients still die of HIV infection and its complications, either in spite of contemporary therapy or because they do not have access to such therapy.

Although the dimensions of suffering for patients with HIV are not unique, some of the sources of suffering within those dimensions deserve emphasis: multiple symptoms, polypharmacy, multiple losses, personal experiences with illness or death related to HIV disease, social stigma and isolation, unpredictable disease course, and the complex and rapidly changing nature of HIV treatment approaches (5,6). Treatment changes have been so rapid and the results (and anticipated results) so broadly marketed, that many individuals with HIV disease do not see disability or death as an option because they expect dramatic new therapeutic advances. Consequently, it is common for these patients to seek health-restoring and life-prolonging therapy until death is near.

The tenacity and will to live is remarkable in many patients with HIV disease. Even the most vulnerable patients who have experienced multiple HIV and HIV-related losses, including the loss of loved ones and support systems, may want “everything done.” As a result, these patients change physicians to seek more aggressive therapy even when told there are no more treatment options. The key skill in managing these situations is to assess patient goals and expectations throughout the course of the disease trajectory. Suffering and quality of life are subjective and can only be determined by the individual, not by the clinician. Consequently, palliative care should be incorporated into the care plan as early in the disease trajectory as it is needed (7,8).

HUMAN IMMUNODEFICIENCY VIRUS AS A CHRONIC ILLNESS

For the majority of patients with access to contemporary therapy, HIV is a chronic illness (Fig. 78-1) (4). Challenges to quality of life occur throughout the course of the illness. These challenges start with the stress associated with the testing process to screen for HIV infection, continue with the various events that emerge during treatment, and culminate with the terminal phases of the disease. For some. patients, this period may be decades in length. Eight landmark events in HIV disease that may cause severe stress and uncertainty (Table 78-1) should be carefully considered when breaking the bad news of a new diagnosis (9). Clinical vigilance for the various manifestations of suffering during the entire continuum of this process is required to offer remedies to improve the quality of life when needed. These remedies include, but are not limited to, state-of-the-art HIV therapies.

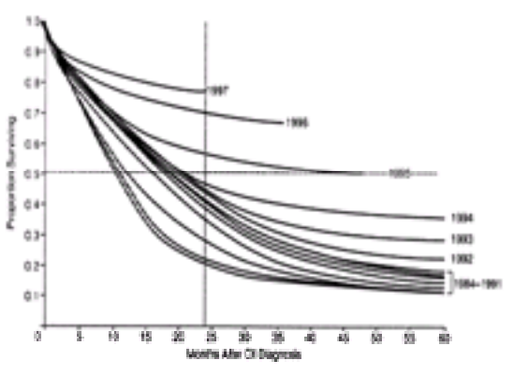

FIGURE 78-1. Probability estimates of median survival after acquired immunodeficiency syndrome (AIDS)– defining opportunistic illness (OI) diagnosis by year of diagnosis, United States, 1984–1997. [From Lee LM, Karon JM, Selik R, et al. Survival after AIDS diagnosis in adolescents and adults during the treatment era, United States, 1984–1997. *JAMA* 2001;285(10):1308–1315, with permission.]

Initial diagnosis of HIV positivity
Initiation of anti-HIV or antiopportunistic infection therapy
Development of acquired immunodeficiency syndrome
Complicating illnesses
Discontinuation of therapies
Pregnancy in patients (or their partners)
Peer group illness and death
Dying and death

TABLE 78-1. THE EIGHT MAJOR POSSIBLE LANDMARK EVENTS IN HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE

The increased survival many patients with HIV experience has led to many sequelae that were not seen earlier in the epidemic. Long-term metabolic, morphologic, and neurological consequences are associated with successful virologic control of the infection. For example, it is unclear whether the hyperlipidemias related to HIV infection will lead to accelerated atherosclerosis and its complications. Without proven medical therapy for the morphologic changes that accompany HIV therapy, these complications may increase the stigmatization of patients (10). These longterm consequences have caused patients and clinicians to question the appropriate time to initiate anti-HIV therapy.

There are other conditions that affect the patient with HIV infection (11). Depression can complicate the course of the disease and adversely impact successful treatment. The risk of financial loss can be overwhelming. The ravages of concomitant substance abuse may add to this suffering.

Chronicity of illness may produce medical, social, and psychological burdens for those living with HIV disease. The need to attend multiple medical appointments for treatment, often at various locations, can be exhausting, particularly for patients experiencing side effects of therapy or if transportation is a problem. Collaboration of health care providers is needed to minimize chaos and to prevent duplication of services. It is not unusual for patients with HIV to be linked to multiple community services; if not well coordinated, however, this can add stress and frustration to the patient, family, and providers. Patients with HIV should be asked whom their best advocate is when multiple “case managers” are involved.

Efforts aimed at managing HIV infection and its consequences must be combined with efforts to relieve suffering and enhance quality of life. This can be complex and requires skills and competencies that may be beyond the usual training of most HIV clinicians. The perspective of palliative care and the expertise and resources of hospice and palliative care programs may provide an opportunity to more comprehensively care for persons living with HIV infection.

A manifestation of this perspective is the development of San Diego Palliative Home Healthcare (SDPHH) in 1998, with the intent of providing “advanced care for advanced disease.” This HIV program is the first, disease-specific, palliative care program of its kind in the San Diego county service area. Critical care nurses are selected and trained as HIV palliative care case managers. Their role is to coordinate all aspects of the patient's care as well as provide direct intermittent care to the patient. Intensive clinical training includes management of anti-HIV treatment, assessment of symptoms and their relationship with adverse effects of drugs, and management of complex pain and symptom syndromes. Interdisciplinary case conferences involve clinical direction from two physicians. One physician is an expert in HIV clinical care and works in a large group practice for HIV disease management, as well as serving as the SDPHH HIV Team Medical Director. Another physician, who is an expert in palliative care, acts as a consultant for patients with complex pain or other symptoms. Both physicians make joint home visits with SDPHH HIV Team members as needed. Ongoing staff support has been essential to maintain the integrity of the team. Every case conference includes time to acknowledge the patients who have been discharged to self-care or who have died, which allows closure for the multiple patient loss issues experienced by the professional caregivers. Strong partnerships have been developed with various community HIV providers. SDPHH has earned a reputation for having a palliative care team with strong clinical skills in HIV disease management. The program has increased access to expert end-of-life care, especially for those who have been unwilling to utilize hospice services. Most important, SDPHH has made it possible for more HIV patients in San Diego County with advanced disease to experience relief of suffering and improved quality of life.

The purpose of this chapter is to provide specific information on the palliative care of patients with HIV not otherwise presented in this textbook. The content is directed to the general clinician, not the specialist in HIV palliative care. The goal is to increase awareness of the need to provide palliative care throughout the course of HIV disease and to discuss approaches to managing common problems.

HUMAN IMMUNODEFICIENCY VIRUS DISEASE—AN OVERVIEW

Human immunodeficiency virus infection is a dynamic process. It has become clear over the last several years that, starting from the time of primary infection, the concentration of virus particles in the blood (the plasma viral load) represents a balance between rapid viral replication and clearance. The viral load is used to help clinicians determine the appropriate time to initiate antiviral therapy, the virologic success of ongoing therapy, and the overall risk of disease progression. This information is combined with the T-helper CD4 count (a measure of the level of virally induced immune compromise) in order to make therapeutic decisions for antiviral therapy and opportunistic infection prophylaxis (12,13).

Even with the most successful suppression of the virus by antiviral therapy, it is now apparent that viral eradication is impossible. All patients have detectable HIV when the most sensitive assays are used. Consequently, HIV is now considered a chronic condition. Three-drug antiviral therapy is cost effective (14). In the best of circumstances, maximally suppressive HIV therapy may delay or prevent progression of the disease. Although the viral load and CD4 count are useful for staging the disease, they do not reliably reflect the degree of symptoms experienced and should not be used to predict the level of distress experienced by a particular patient.

The presence of the virus, despite suppression of virologic replication, initiates cytokine activation and contributes in part to the constitutional symptoms of HIV disease. The other factors that contribute to constitutional symptoms, such as fatigue and sweats, are poorly understood and need to be approached clinically with a consideration of multiple possible causes, including the virus, opportunistic infections, metabolic issues, hematological conditions, and antiviral therapy.

At the beginning of the epidemic, the average survival for someone with acquired immunodeficiency syndrome (AIDS) was 18 months. Now, with proper treatment, a normal life expectancy may be possible for many (4). Our successes in treating HIV have resulted in an increasing prevalence of people living with HIV and a need for more attention to non-HIV routine health maintenance.

Populations at Risk

Because of the nature of HIV transmission, the disease has adversely affected numerous populations. These populations include men who have sex with men (MSM), women, sex workers, substance users, the poor, and minority populations. The development of sensitivity and increased awareness of cultural differences is required if they are to be most effectively assisted (15).

MSMs comprise a decreasing proportion of those with HIV in the United Sates They may or may not identify themselves as homosexual, gay, or bisexual. They frequently have various less traditional family associations. In addition, their family may either be estranged or unaware of their lifestyle or HIV status. An increased awareness for the usual sexually transmitted diseases among MSMs is critical, particularly because of the recent rise of syphilis and rectal gonorrhea in this population (16,17). In addition, an awareness of the increased incidence of human papilloma virus and the development of anal cancer is important in this group (18).

Women comprise 24% of those reported with AIDS. A disproportionate number of these women are African-American and Hispanic. Intravenous drug use and heterosexual transmission, including sex for money, are the leading risk factors for acquisition of HIV by women. There are numerous psychosocial stresses these women with HIV experience. These include the need for help with child care, less access to health care, and issues with their significant other because of their HIV status.

Although the exact proportion of men and women with HIV who are commercial sex workers is not known, this population deserves special mention. This group, as a whole, tends to abuse substances more often and has less stable living situations. Although complete adherence to the recommendations for safer sex and substance use is rare, a harm reduction approach might result in fewer consequences resulting from these practices. This is a special. population for whom increased psychosocial support and utilization of community resources designed to assist this group will enhance the therapeutic success.

Substance abuse, as a whole, is not only a risk factor for the acquisition of HIV infection but serves as a harmful coping strategy for those experiencing distress because of their HIV status. The consequences of this strategy include the toxic and infectious complications of drug use as well as the deleterious effects on medical adherence and follow-up. Although abstinence may be preferred, a harm reduction approach to minimize the complications of substance abuse might be more successful for many. The attitude of the clinician with regards to these issues can seriously affect the level of trust and disclosure that the patient offers.

The poor and minority populations who are underinsured but overrepresented among those with HIV have a higher risk of receiving no or less care for their disease (19). This places them at a higher risk for disease progression and incomplete treatment of their symptoms. Although federal entitlement programs such as the Ryan White Care Act and the AIDS Drug Assistance Program make treatment available to the underinsured, there are still many who are eligible but do not access care. Further, the regional differences in program content leave certain aspects of care unavailable. An increased cultural awareness for these groups by the clinician can be a great asset to those served.

Contemporary Anti–Human Immunodeficiency Virus Therapy

The advent of highly active antiretroviral therapy with multiple drugs used in combination has dramatically changed the natural history of HIV since 1995. A detailed discussion of antiretroviral therapy is beyond the scope of this chapter, but a few comments can place the field into a contemporary perspective. Except for the approximately 5% of patients who are nonprogressors, it would appear that the remainder will ultimately experience increasing viremia and immune compromise (20).

Because of the problems associated with antiviral treatment, there has been a change in recommended therapy from “hit early, hit hard” to a more conservative postponement of therapy (11). This change has come from the recognition that many factors influence therapeutic success such as the effects of pill burden, the need for >95% adherence for maximal success, the long-term metabolic effects of therapy, and the challenges of treating patients with antiviral resistant virus (21). Despite the development of viral resistance assays to help guide the choice of drugs, the long-term benefit from using them is, as yet, unclear. Coupled with the limited armamentarium of antiviral agents, these observations support the advice to wait longer to initiate therapy.

At the time of this writing, there are 16 licensed drugs to treat HIV. Unfortunately, intraclass cross-resistance limits treatment options. Clinically significant adverse effects of the medications include nausea, bloating, diarrhea, rash, hepatic and renal dysfunction, neuropathy, cytopenias, and sleep disturbance. Careful attention to food and water requirements and the varied drug interactions is required. It is for these reasons and others that detailed knowledge about the medications or consultation with an HIV specialist is strongly recommended when a generalist cares for one of these patients.

Although progression of the disease can be prevented with the newer medications, this success is not without cost. There are a number of HIV-associated conditions that appear to be the consequence of metabolic disturbances resulting from the virus and/or the therapy used. These conditions include neuropathy, lipodystrophy, hyperlipidemia, and hyperglycemia. These conditions may be due to mitochondrial dysfunction and may be responsible for a large part of the morbidity associated with HIV (22).

It should be no surprise that structured treatment interruptions are being investigated to see if intermittent treatment may reduce toxicity without compromising control of the disease. Although this approach is purely experimental, it has been embraced by the HIV-infected community as a response to the significant adverse effects of therapy. This area of HIV medicine requires careful consideration of quality of life issues balanced with those of virologic control.

The ultimate goal of therapy needs to be customized by the health care professional and the patient. Many times, palliative antiretroviral treatment, as opposed to maximal viral suppression, may be more appropriate for patients with viral resistance precluding such control, and in those unable to tolerate a “complete” regimen.

Comorbidity

Among many possible comorbidities (cancer among them), it is important to mention the contribution of chronic hepatitis B and C virus infection to the overall morbidity of many patients with HIV infection (23). Not only can these conditions increase the chance of hepatotoxicity from multiple medications, but they may also be major causes of the constitutional symptoms that patients with HIV experience. With the new methods of treating these coinfections, selected patients may now benefit from cotreatment of their viral hepatitis. It is important to point out that all the symptoms a patient experiences may not be directly or indirectly related to HIV infection. Patients must be carefully evaluated for comorbid conditions.

HUMAN IMMUNODEFICIENCY VIRUS PALLIATIVE CARE

Setting Goals

Understanding the goals of the individual infected with HIV disease is the essential first step in palliative care. There are a range of possible goals. Cure, prolonging life, relief of symptoms, avoiding hospitalization, and putting affairs in order before anticipated death are but a few. There may be multiple goals. They may be contradictory. The process of setting goals, including a discussion of patient values, also serves to enhance the clinician-patient relationship through improved understanding of the patient by the clinician (7).

Goals are likely to change over the course of a lifetime or an illness. It is important that a conversation about goals occurs early following the diagnosis of HIV infection so that appropriate palliative care techniques may be applied throughout the course of illness. None of the palliative interventions discussed in this chapter will decrease longevity or hasten death.

Palliating Physical Symptoms

General principles of management guide the palliation of physical symptoms. Three of those principles deserve particular mention.

Communication

One of the most critically important tools is good communication. Without it, physical symptom assessment will be, at best, inaccurate and, at worst, impossible. In addition to assessment, communication serves a teaching and reassuring role. Given the myriad possible implications of a new or worsened physical symptom, one of the most important roles for clinicians caring for patients with HIV infection lies in telling them what they do not have. For example, good communication can reassure anxious patients that their common cold is not *Pneumocystis pneumonia* and that the bruise on their leg is not Kaposi's sarcoma (24).

Think Critically

A common pitfall in managing persons with HIV infection is to attribute all symptoms to the underlying HIV disease. Persons with HIV may, like cancer patients, have other etiologies for their symptoms that may be readily treated and resolved. Many clinicians abandon the problem-solving diagnostic approach used in other areas of medical practice when caring for someone with advanced-HIV infection. This is unfortunate because retaining this approach is essential for effective symptom management.

Prevent Problems

Good palliative care seeks to both anticipate and prevent likely events. Prescribing medication to prevent common symptoms is critical. Regular dosing of medication in order to prevent symptom recurrence should follow initial treatment of presenting symptoms (25).

Hematological Manifestations

Hematological abnormalities are extremely common in HIV disease and can pose a significant threat to the quality of life of the person affected. These abnormalities generally manifest as anemia, leukopenia, and thrombocytopenia resulting from direct or indirect effects of HIV, opportunistic infections, or medications used in management of HIV. A detailed description of the differential diagnoses and management of these conditions has been reviewed elsewhere (26,27). What follows is a general discussion of the hematological effects seen with HIV.

Anemia

Anemia is the most frequently observed hematological abnormality in HIV infection. It may cause fatigue, dyspnea, altered mentation, headaches, and cold intolerance (28). Anemia has been correlated with decreased survival and its resolution with an improved prognosis in HIV disease. Usually, the anemia of chronic inflammatory block is responsible. However, other hypoproliferative states may be responsible: medications (Table 78-2), marrow infiltration by tumor (e.g., lymphoma) or opportunistic infection, gastrointestinal bleeding, and vitamin B_{12} or folate deficiency. Rarely, anemia may result from autoimmune hemolytic anemia, drug-induced hemolysis from glucose-6-phosphate deficiency, or disseminated intravascular coagulation.

Drug	Anemia	Neutropenia	Thrombocytopenia
Amphotericin	X	X	X
Anti-neoplastic chemotherapy	X	X	X
Anti-RhD	X	X	X
Cidofovir	–	–	X
Flucytosine	X	X	X
Foscarnet	–	–	X
Ganciclovir	X	X	X
Interferon	X	X	X
Pentamidine	–	–	X
Primaquine	X	–	–
Pyrimethamine	X	–	–
Pyrazinamide	X	–	–
Rifabutin	–	–	X
Rifampin	–	–	X
Trimethoprim-sulfamethoxazole	X	X	–
Trimetrexate	X	X	–
Zidovudine	X	X	–

TABLE 78-2. HEMATOLOGICAL EFFECTS OF MEDICATIONS USED IN HUMAN IMMUNODEFICIENCY VIRUS DISEASE

The approach to treating anemia requires evaluation for its cause and treatment of the underlying condition. If causative medications are identified, they should be eliminated, if possible. Transfusion requirements may be reduced or eliminated with the use of recombinant human erythropoietin. If the endogenous erythropoietin level is <500 units/ml, recombinant human erythropoietin may be dosed at 50–100 U/kg subcutaneously three times a week. Recent studies have shown that once weekly injection of the total dose is as effective. Generally, maintaining the hemoglobin concentration above 10 g/dl reduces symptoms related to anemia. However, it is important to mention that the symptoms may be multifactorial and may not resolve with treatment of anemia. Further, the baseline functional status of patients, their underlying conditions, and their goals are important to consider before treatment is applied to a low hemoglobin level.

Neutropenia

A lower than normal leukocyte count is quite common in HIV infection. This is most frequently due to a combination of lymphopenia due to CD4 reduction and neutropenia. The frequency and degree of neutropenia increase as HIV disease progresses. The causes of neutropenia may result from HIV infection itself, medications (Table 78-2), and concomitant infections. The neutropenia related to HIV alone is associated with myeloid precursor dysregulation, lower levels of granulocyte colony-stimulating factor and anti-granulocyte antibodies. The risk of infection increases when the absolute neutrophil count (ANC) is <500, and most providers consider some intervention when the ANC is <1000 (29).

Treatment of an identified condition contributing to the lowered ANC is always the first approach. The availability of recombinant granulocyte colony-stimulating factor has made it possible to continue some myelosuppressive therapies without the risk of complications from neutropenia. However, when multiple medications that cause neutropenia are being used, some adjustment of the medical regimen is usually required. This situation most frequently arises during the treatment of cytomegalovirus (CMV), toxoplasmosis, *Pneumocystis carinii*, and lymphoma.

Utilization of nonmyelosuppressive medications is preferred when possible, but granulocyte colony-stimulating factor 1–5 mg/kg/d usually elevates the ANC to eliminate any risk. After the ANC is >1000, the dose and frequency may be adjusted as indicated by the neutrophil response.

Thrombocytopenia

Thrombocytopenia is quite common in HIV infection, but hemorrhage from reduced platelets is not. Bleeding is rare because the counts are usually only modestly reduced. When the etiology of the thrombocytopenia is due to increased destruction, the remaining platelets tend to be younger and more functional.

The most common causes of thrombocytopenia associated with HIV result from decreased production related to the virus, marrow invasion by tumor or opportunistic infection, and medication effects on the megakaryocytes (Table 78-2). Increased destruction can also cause reduced platelets in the setting of infection, immune-mediated destruction, thrombotic thrombocytopenic purpura, or disseminated intravascular coagulation. After reviewing and eliminating medications and ruling out increased destruction by clinical evaluation and examination of the blood smear, the question is usually whether the thrombocytopenia is immune-based or due to marrow infiltration. If the clinical picture or marrow examination excludes the latter, immune thrombocytopenia caused by HIV is generally the cause.

Treatment of HIV-associated immune thrombocytopenia is initially approached by antiretroviral therapy. Older studies had positive responses using zidovudine, but it is unclear whether this was because this drug has a unique effect on platelet production or whether the limited choices of agents at the time led to this conclusion (30). Adjunctive therapies with danazol, intravenous immune globulin, anti-RhD, and prednisone can also help. The plasma-based treatments are effective but can be expensive and must be continued in order to maintain the remission. However, the long-term use of corticosteroids in these patients has to be balanced with the higher risk of opportunistic infection and progression of Kaposi's sarcoma. Splenectomy is rarely needed and places the patient at high risk of the usual infectious complications accompanied by asplenia. Platelet transfusions should be reserved for cases where life-threatening hemorrhage is likely and other more long-term treatments are planned as long as the patient's wishes and clinical situation warrant such therapy.

Constitutional Symptoms (Anorexia/Cachexia, Fatigue)

Anorexia (decreased appetite) and cachexia (weight loss) occur in as many as 70–90% of patients with AIDS (31). Cachexia is an independent risk factor for mortality. Advanced HIV infection is associated with weight loss in excess of 5% of the usual body weight. Although this may ultimately affect a majority of patients with AIDS, it may also be an early finding (i.e., early in the epidemic, 17% of patients had wasting as their AIDS-defining illness, and 24% will have it as a component of their presentation). The catabolic state of these patients also potentiates their already present immune deficiencies, thus increasing the risk of opportunistic infection (32,33 and 34).

The patient's anxiety about the meaning of weight loss and fatigue, as well as the loss of pleasures associated with eating and activity, may have a profound impact on quality of life.

Hellerstein and colleagues have implicated inflammatory cytokines, such as interleukin-1 and tumor necrosis factor, as causal mediators of anorexia-cachexia in AIDS (32). Opportunistic infections, particularly disseminated *Mycobacterium avium intracellulare*, have been implicated in causing fever and weight loss (35). Other common causes or contributors to anorexia/cachexia and fatigue include medications, such as the antivirals, sulfonamide antibiotics, and metronidazole, and endocrine disorders (including hypogonadism and rarely hypothyroidism), anemia, and depression.

Diminished food intake in patients with HIV infections may be due to lesions of the mouth, pharynx, or esophagus related to specific medications or associated with nutrient malabsorption or systemic infections. Several intestinal parasites, such as cryptosporidium, Isospora, and microspora, are major pathogens in AIDS and are clearly associated with intestinal dysfunction (34).

As in managing any symptom, before discussing specific therapy, patients should be asked whether or not they perceive their anorexia, cachexia, and fatigue to be problematic. It is not infrequent that this symptom complex is concerning to family or friends rather than the patient. If not, interventions may be foregone in accord with the wishes of the patient.

General measures are pursued first. These usually include a dietary consultation to identify foods that are likely to be attractive and appetizing as well as high in calories. Specific seasoning of food may be helpful. Dietary restrictions of calories, sweets, or sodium make no logical sense. A physical therapy consult for an evaluation and regimen to build endurance should be considered for patients with fatigue.

The patient's medication list should be evaluated for medications that may be contributing to anorexia and appropriate changes made where indicated. Specific conditions that are correctable should be searched for diagnostically, including opportunistic infections.

Anemia may be treated with erythropoietin injections or transfusion. Depression may be treated with psychostimulants or antidepressants. Hormonal replacement may be indicated. Hypogonadism should be treated with testosterone.

Growth hormone and anabolic steroids for patients with weight loss may also be effective. These modalities have been associated with increased appetite, energy, and lean body mass, which has been correlated with increased survival. Testosterone (200 mg i.m./wk or 5 mg topical gel/day) with or without oxandrolone 10 mg twice a day has been very helpful for lean body mass increases and an increase in functional status in men. Human growth hormone also can have these effects at a higher cost. It is given as a daily injection of 3–6 mg and is associated with a high incidence of reversible myalgia, arthralgia, carpal tunnel syndrome, and edema. Both approaches work best in the setting of optimal nutrition and a moderate exercise program.

Appetite stimulants, including corticosteroids, progestational drugs, and dronabinol, may or may not be helpful. They have been associated with only fat mass accumulation that has no effect on the overall prognosis but may have a palliating effect on the patient. Stimulants, such as alcoholic beverages or caffeine-containing beverages, may be helpful if given 30 minutes before meals.

Corticosteroids (e.g., dexamethasone, prednisone) are associated with a short-term increase in appetite (approximately 4 weeks) without significant weight gain. Some clinicians fear the use of these drugs in patients with HIV in view of the underlying immune deficiency. However, in patients with advanced HIV infection in whom a generalized improvement in well-being and stamina is desired, and for whom long-term therapy is not contemplated, corticosteroid therapy may be useful. Dexamethasone in a single morning dose of 2–6 mg may be effective, although a higher dose may be required.

Progestational agents like megestrol acetate (Megace) have been proven effective in improving appetite, with maximal weight gain usually demonstrated within 8 weeks of starting the medication in patients with AIDS (33,36). As a dose response with respect to weight gain has been demonstrated, it is best to begin therapy with 800 mg/day. If there is a response, the dose can be titrated to the smallest dose that maintains the desired effect. The drug is expensive and has been associated with hyperglycemia due to its glucocorticoid effect, and impotence in men from its inhibition of testosterone secretion. The latter effect can be prevented with concomitant testosterone therapy. Sudden withdrawal of megestrol acetate can precipitate adrenal crisis due its suppression of the adrenals.

Dronabinol (Marinol) and tetrahydrocannabinol (THC) have been shown to increase appetite and weight in AIDS patients (37,38 and 39). The therapeutic effect may not be seen for up to 4 weeks. The starting dose is 2.5 mg twice a day before meals, which is gradually increased until the desired effect is achieved. Clinically effective doses of dronabinol are associated with euphoria or dysphoria in some patients, particularly the elderly. Patients with a history of smoking marijuana are more likely to tolerate the drug well. Smoking marijuana may be more effective because absorption of oral. THC has been found to be erratic. Smoking, however, may place the HIV patient at risk for possible injury to the lung and immune system, with increased episodes of *Pneumocystis carinii*, bacterial, and fungal *(Aspergillus*) pneumonias (37).

Prokinetic medications, such as metoclopramide (Reglan), may help with symptoms of anorexia related to early satiety. Enteral nutrition supplements beyond optimal dietary management improve nutritional status only marginally, and are not well tolerated in patients with advanced HIV disease. If chosen, oral supplements should be lactose-free to minimize diarrhea and abdominal cramping.

Total parenteral nutrition is only recommended for HIV patients who have one of four conditions and are otherwise well: (a) severe refractory diarrhea associated with progressive weight loss and malnutrition, (b) persistent intolerance to enteral feeding in the absence of any acute, remediable, AIDS-related condition, (c) persistent severe gastrointestinal malabsorption, or (d) intraabdominal pathological condition resulting in indefinite continuous mechanical bowel obstruction. In advanced HIV disease, however, in the absence of one of the four conditions just named, total parenteral nutrition rarely helps the symptoms of fatigue and anorexia for which it is offered (8).

A care plan with short and long-term goals should be formulated and useful interventions continued, while those that are not effective are discontinued in a timely manner. For patients with advanced HIV disease, or those who fail interventions to correct anorexia and cachexia, clinicians can educate patients and families about what to expect and about the emotional meaning of weight loss and feeding. At this time, it is usually best to stop weighing the patient, thus removing another focus on a numerical value.

Fatigue is usually not easily overcome by rest. Symptomatic treatment includes planning and pacing activity and promoting adequate sleep, nutrition, and rest. An occupational therapy consultation may be helpful. Rest periods, however, should be differentiated from naps. Napping throughout the day may, in fact, increase fatigue.

Environmental manipulation is helpful. Thoughtful placement of phone, medications, drinking water, and other essentials decreases energy expenditure. Because immobility promotes fatigue, at least some exercise is helpful, whether it is passive or active (40,41 and 42).

Psychostimulants such as methylphenidate (Ritalin) 2.5–5.0 mg morning and noon, and dextroamphetamine (Dexedrine) 10 mg daily may be given to reduce fatigue (43). Medication should be given in the morning to prevent interference with normal sleep.

Pain

Pain may be as prevalent in patients with HIV as it is in patients with cancer (44,45). The approach to pain in the patient with HIV is not fundamentally different from that in the patient with cancer (46). Many different pains are found in patients with advanced AIDS, and studies show that these pains are consistently underdiagnosed and undertreated. A majority of AIDS patients have more than one type of pain, and the prevalence of pain increases as the disease progresses (44,45,47,48).

Good pain management relies on good pain assessment, including an adequate pain history and an ongoing evaluation of the response to analgesics.

Neuropathic pain occurs in 30–40% of HIV patients (46). Although some of the medications used in the management of HIV disease may cause peripheral neuropathy, this condition can also develop from the effects of HIV on the nervous system itself.

Patients frequently describe the pain of peripheral neuropathy as burning, shooting, numbness, or like pins and needles. Findings on physical examination that support the diagnosis of neuropathy pain are allodynia (a usually nonpainful stimulus like light touch provokes the pain), hyperesthesia, numbness, absent reflexes, or color changes in the affected area. Diagnostic tests, such as electromyography, are not generally necessary to confirm the diagnosis of painful peripheral neuropathy. Pain management may begin after an adequate history and physical examination have been completed.

The relief of pain in patients with AIDS is largely approached by pharmacological methods. Treatment should optimize the use of nonopioid, opioid, and adjunct analgesics. However, this does not minimize the adjunctive roles that explanation, empathy, understanding, and nonpharmacological analgesic therapies play (50). Psychological factors, such as low mood, fear, and anxiety, should be actively addressed.

In contrast with nociceptive pain, the control of neuropathic pain frequently requires adjuvant medications, such as antidepressants, anticonvulsants, and others, in addition to opioids. No one class of medication, or specific medication, is effective in every patient. Adverse effects and drug interactions often influence the choice of agents. If there is a strong clinical suspicion that the neuropathic pain is due to medications, these should be stopped so that the syndrome does not progress further. It should be noted that the neuropathy might progress for a month or two after discontinuation of the offending agent(s) before improvement is seen from drug discontinuation.

The tricyclic antidepressant, amitriptyline, is the most studied adjuvant for neuropathic pain. However, all of the tricyclics are analgesic. Although these analgesic effects, like the antidepressant effects, are presumably mediated through monoaminergic mechanisms, depression is not prerequisite for analgesic efficacy. Analgesia is frequently observed at dosages considered to be subtherapeutic for the treatment of depression. Desipramine and nortriptyline are more commonly prescribed because of fewer adverse effects (49,50).

Serotonin selective reuptake inhibitors may be less effective than the tricyclic antidepressants for neuropathic pain. They may have a role in the treatment of concurrent depression that can worsen pain. Venlafaxine (Effexor) has both serotonergic and adrenergic effects. This may explain some reports of its effectiveness as adjunctive analgesic therapy for neuropathic pain.

Anticonvulsants are also analgesic for neuropathic pain. Gabapentin (Neurontin) is widely used and has been proven effective in diabetic peripheral neuropathy and in postherpetic neuropathy. Carbamazepine (Tegretol), valproic acid (Depakote), and phenytoin (Dilantin) have all been described to have analgesic effects in

neuropathic pain.

Methadone is an opioid with unique characteristics that could theoretically enhance analgesic effects in neuropathic pain (51). Some have observed that patients with severe pain respond better to methadone than other opioids at equianalgesic doses. This has been attributed to the N-methyl-D-aspartate antagonist activity of the D-isomer of methadone. Commercially available preparations of this medication consist of a racemic mixture of levo and dextro isomers. The levo isomer has analgesic activity at opioid receptors.

Historically, the use of methadone has been eclipsed by long-acting preparations of opioids with more predictable pharmacokinetics. As an analgesic, methadone was considered a difficult medication to titrate due to its long half-life and concern that it is lipophilic and likely to be fat deposited. Now, however, clinicians are expressing renewed interest in methadone, particularly for HIV patients with mixed pain syndromes (both neuropathic and nociceptive). Their lower body fat stores make fat deposition less of a problem.

Most current conversion tables list 20 mg of methadone as dose equivalent to 30 mg of morphine. However, new data suggests that methadone is at least ten times as potent as morphine when converted at high doses (51). Conversion from the previously prescribed opioid may be done safely in 3 days by decreasing the dose of the previous opioid, one-third each day, and increasing the dosage of methadone by one-third of the target final dose each day (E. Bruera, personal communication).

In the recent experience of the authors, methadone is frequently effective for neuropathic pain in HIV patients, particularly those who have mixed pain syndromes. The stigma associated with methadone, related to its use in addiction medicine, takes work to overcome with some patients, but this is usually worth the effort in improved pain management (52).

A past or present history of recreational drug use raises an additional concern in the treatment of pain in patients with AIDS. Although this is treated as a general topic elsewhere in this text (see Chapter 41, Substance Abuse Issues in Palliative Care), a few remarks are in order. Most important, nonopioids should not be substituted for opioids in the management of pain merely because of a history of substance abuse (46). When treating patients with HIV infection and a history of opioid abuse, the clinician should anticipate using larger doses of the opioid analgesics than usual because of the incipient tolerance that may be present. Concerns regarding drug diversion or abuse need to be openly discussed with the patient. Contracts may be needed to clarify issues and expectations.

Nausea and Vomiting

Nausea is an unpleasant sensation that may be activated by any or all of four primary mechanisms involving stimulation of the chemoreceptor trigger zone (CTZ), vestibular apparatus, gastrointestinal tract, and cortical areas. In many HIV patients, the cause of nausea is multifactorial and will require combination antiemetics to manage.

One of the most common mechanisms is stimulation of the CTZ in the fourth ventricle. Because of the polypharmacy that almost always accompanies the treatment of a patient with advanced HIV infection, drug-induced nausea mediated through this mechanism is exceedingly common. Medications that commonly stimulate this mechanism include antiretrovirals, opioids, and antibiotics. Although discontinuing or changing these medications may prove difficult, treating this mechanism with inexpensive dopamine antagonists (promethazine, haloperidol, droperidol, metoclopramide) or more expensive serotonin antagonists (ondansetron, granisetron) may be effective in relieving nausea (53).

The vestibular apparatus is stimulated in motion sickness and as an initial effect of opioids. Treating this mechanism with an antihistamine (diphenhydramine) or anticholinergic (scopolamine) is usually effective. Histamine and acetylcholine receptors are also implicated in the CTZ.

Patients who describe early satiety, or who report persistent nausea and vomiting only after eating, may be suffering from an HIV-associated diffuse gastroenteropathy caused by dysmotility, mucosal CMV infection or infiltrative tumor (Kaposi's sarcoma or lymphoma). Nausea and dysmotility may also be a result of constipation. In addition to usual management of constipation, prokinetic agents like metoclopramide may be helpful (54).

Nausea caused by central cortical mechanisms may respond to multiple interventions. Benzodiazepines (lorazepam, diazepam) are probably effective through their anxiolytic and amnestic effects. Corticosteroids have broad antiemetic properties that are poorly understood. These effects are not explained by the treatment of nausea due to increased intracranial pressure from tumor or infection. Tetrahydrocannabinol, dronabinol (Marinol), or marijuana have antiemetic effects that relate to diffuse cortical effects that are poorly understood.

For many cases of nausea in patients with HIV disease, the precise etiology is either unclear or multifactorial. In these cases, empirical therapy with combination antiemetics is appropriate. Choices are best directed by a rational combination of antiemetics with different mechanisms of action. For example, a combination of diphenhydramine (Benadryl), which is effective at the sites of the vestibular apparatus and vomiting center, metoclopramide (Reglan), which is prokinetic, and a dopamine antagonist, effective at the CTZ, and dexamethasone, which is effective on central cortical factors, has been widely advocated as an empirical approach. This combination may be administered in an oral liquid preparation, a suppository, or as a parenterally administered infusion either intravenously or subcutaneously.

In cases of nausea and vomiting due to bowel obstruction, octreotide (Sandostatin) decreases gastrointestinal secretion, promotes intestinal water absorption, and prolongs gut transit time. This medication is given subcutaneously either in a continuous infusion or intermittently three times per day. A starting dose of 0.3 mg in 24 hours may be titrated daily to effect (usually no more than 0.8 mg per day) (54,55).

Diarrhea

Up to 90% of patients with HIV disease will experience diarrhea at some time during their illness. Common causes of diarrhea include infections, medications (antivirals, magnesium compounds in antacids, antibiotics, nonsteroidal antiinflammatory drugs, iron preparations, metoclopramide, and theophylline), tumor invasion (lymphoma and Kaposi's sarcoma), and lactose intolerance (8).

Although it is important to investigate causes, attempts to control the symptom can be instituted while the workup is proceeding. In the absence of bloody diarrhea and/or fever, prudent evaluation begins with stool studies and administration of antidiarrheal medication. If the diarrhea is unresponsive to modest symptomatic therapy (loperamide) and the stool studies nondiagnostic, the workup should then proceed to esophagogastroduodenoscopy with biopsy and colonoscopy with biopsy.

Definitive treatment should be based on stool study results, when available and helpful, but sometimes empiric antibiotic treatment may be initiated. Consideration of a combination of ciprofloxacin (Cipro) and metronidazole (Flagyl) may be indicated.

Nonpharmacological interventions include oral rehydration with balanced electrolyte concentrations and glucose. Avoiding milk products is advisable because a secondary lactase deficiency may exacerbate diarrhea. Supplemental digestive enzymes and calcium-containing antacids may also be helpful. Consideration should always be given to protecting the skin in incontinent patients and multiple barrier ointments are available.

Absorbent medications (pectin), adsorbent medications (kaolin), and attapulgite (Kaopectate) and psyllium do not affect diarrhea *per se*. However, turning frequent watery stools into less frequent semiformed stools may enhance comfort. Bismuth subsalicylate (Pepto-Bismol) contains aspirin and is useful for mild diarrhea, especially if there are abdominal cramps.

Loperamide (Imodium) is an opioid used for its constipating effect. Because of minimal systemic absorption, its effects are local. It is 50 times more potent than codeine. Morphine as an antidiarrheal has the additional benefit of increasing tone in the anal sphincter. Diphenoxylate with atropine (Lomotil) is a combination antidiarrheal that includes an opioid to decrease motility and an anticholinergic to decrease intestinal transit and secretion.

Refractory large volume diarrhea responds to octreotide (Sandostatin). A panel of U.S. physicians has recommended that patients who do not respond to 0.5 mg subcutaneously three times a day after 1 week have their therapy stopped. Those who respond to this regimen are tapered downward after 2 weeks by 0.1 mg per injection for 1 week, and then by 0.05 mg per injection in subsequent weeks, to the minimally effective octreotide dose (54).

Neurocognitive Symptoms (Dementia, Delirium, Depression)

Late-stage HIV is associated with a progressive dementia characterized by a loss of short-term memory, mental slowing, decreased concentration, and poor judgment not unlike the dementias seen in geriatric populations. For this reason (among many), it is suggested that advance directives be identified early in the course of HIV illness (56). The dementia is related to HIV infection and can be reversed or slowed with anti-HIV therapy.

By contrast, delirium is an acute change in global cognitive abilities. For appropriate patients, reversible causes of delirium should be sought. The resolution of an acute delirium leads to vastly improved quality of life as well as length of life. A contrast-enhanced magnetic resonance imaging of the head is an important first step. Enhancing lesions are most often toxoplasmosis (90%), although primary central nervous system lymphoma and other causes are possible. If the magnetic resonance imaging scan is not diagnostic, a lumbar puncture should be performed. Cryptococcal meningitis, CMV encephalitis, neurosyphilis, and tuberculous meningitis may present with no more than subtle changes in personality, mood, or progressive fatigue.

Medications that may cause or contribute to acute delirium include opioids, beta-blockers, anticholinergics, corticosteroids, anticholinergic medications, efavirenz (Sustiva), and metoclopramide. Dehydration may also be responsible. Delirium in a patient with diarrhea and resulting electrolyte abnormalities may resolve with rehydration.

Pharmacologic management of the symptoms of delirium relies on neuroleptics. Haloperidol (Haldol) 0.5–5.0 mg every hour until symptoms are settled, then every 6 hours for maintenance is indicated for the symptomatic management of patients presenting with agitated, hyperactive forms of delirium, including psychomotor agitation, delusions, and/or hallucinations. If sedation is a primary goal, then a more sedating neuroleptic may be used [e.g., chlorpromazine (Thorazine)]. The neuroleptics should be considered a temporary measure while other strategies to reverse the delirium are instituted, such as opioid rotation, rehydration, or the management of metabolic or infectious complications. If the overall goal is sedation and no efforts to reverse the delirium are to be attempted, such as in terminal delirium, then benzodiazepines may be used for their sedating, amnestic, antiepileptic, and muscle-relaxing properties.

A frequently encountered challenge is the patient who was previously independent and is now demented and unable to care for himself or herself. Social work intervention is invariably required. The patient's safety must be ensured. Often this means that 24-hour monitoring is required. A change in domestic arrangements or even a move to a nursing facility may be required.

Depression is prevalent in patients with HIV infection (56,57). It is often difficult to diagnose in advanced HIV disease because the somatic criteria for the diagnosis may be a result of the HIV disease progression. Therefore, in order to diagnose depression, clinicians must have a high index of suspicion and rely on psychological features.

Unfortunately, many patients and clinicians feel that depression is a normal or expected response in patients who know they have a life-threatening disease. For this reason, depression is underreported, underdiagnosed, and undertreated in HIV patients. This is a prominent risk factor for suicide (57,58). Depression, unlike sadness, is not a normal response to illness.

Once suspected or diagnosed, a therapeutic trial of treatment is indicated. Combining supportive psychotherapy and medication is frequently effective. The serotonin selective uptake inhibitor group of antidepressants is effective and has fewer side effects than older tricyclic agents. Citalopram has the fewest drug interactions and adverse effects in the chronically ill. However, a lag phase of several weeks occurs before onset of relief should be expected (59).

For patients in whom a faster response is desired, a psychostimulant (methylphenidate, dextroamphetamine) may be helpful to relieve symptoms of hopelessness, helplessness, and despair in a matter of days (60). Psychostimulants can be combined with other antidepressants. In this case, they are continued until the end of the lag phase, and then the patient is tapered off the psychostimulant. Psychostimulants should only be taken in the morning to prevent insomnia. Use of these drugs should be carefully considered in those patients with a history of stimulant abuse.

Dyspnea

Dyspnea is the sensation of shortness of breath. In patients with HIV disease, dyspnea and cough usually occur because of infections: bacterial, viral, protozoal, or fungal. Infiltrative processes, such as Kaposi's sarcoma or lymphoma, may also be responsible. Other common conditions, such as congestive heart failure, bronchospasm, pulmonary embolism, pleural effusions, and drug reactions, should be considered. Anemia is an often present but overlooked factor. Anxiety nearly always coexists with dyspnea and should be considered an exacerbating factor.

Symptomatic management and therapy directed at the cause can be instituted simultaneously. Several nonpharmacological interventions are helpful. Instructing the patient in pursed-lip breathing and elevating the patient's head are useful. The environmental air should be cool and humidity should be low. A slight cool breeze from a fan blowing on the patient's face is helpful. Activity should be limited to what is necessary and rest periods should be planned. Regular and frequent oral care helps decrease discomfort related to dry mouth (61).

Many patients describe relief of dyspnea when oxygen is administered. Patients may describe relief even when their hemoglobin oxygen saturation is normal in the absence of additional oxygen. This may be due to psychologic factors and the placebo effect because oxygen is a potent symbol of medical care.

Bronchoconstriction may be present in HIV patients without a previous history of asthma. A clinical trial of a bronchodilator, such as albuterol, may bring significant relief.

Opioids act both centrally and peripherally to diminish the sensation of dyspnea. They may also be administered by inhalation. Clinicians may be reticent to prescribe opioids at the same time they are attempting to treat a lung infection, owing to exaggerated fears of respiratory depression. Doses of opioids that relieve dyspnea do not cause central respiratory depression. This highlights a critical aspect of dyspnea management: the patient's self-report is used as the primary clinical indicator of relief. It is incorrect, and may lead to therapeutic misadventure, if opioids are titrated to respiratory rate rather than self-report of relief.

Dyspnea is one of the most frightening sensations that a patient can experience. In many, anxiety plays an important role in the symptom complex. For intermittent anxiety, an intermediate-acting benzodiazepine (lorazepam, 0.5–1.0 mg orally every 4 hours) may help. When anxiety is constant, a longer acting benzodiazepine (diazepam, 2–5 mg orally three times daily) may be indicated.

Oral Problems

Dry or sore mouth is common in HIV patients. Oral hairy leukoplakia is commonly seen on the lateral border of the tongue and correlates with advanced HIV disease, but is usually not symptomatic. Kaposi's sarcoma, which is commonly found on the palate but can involve any mucosal site, may respond to regional radiation therapy or systemic chemotherapy (62).

Painful oral lesions include those caused by thrush (candidiasis), herpes simplex virus, aphthous ulcers, and CMV. Oral candidiasis may present as a reddened mucosa without demonstrating the more familiar white plaques. Herpes may be present without the characteristic gray pustules on an erythematous base. Swabs and/or biopsies may be the only way to confirm the diagnosis. Treatment may be general with 2% viscous lidocaine topically for pain, or specific with nystatin oral solution, ketoconazole, or fluconazole for oral candidiasis, or acyclovir for herpetic infection. Oral aphthous ulcers respond to topical corticosteroid such as triamcinolone in Orabase or dexamethasone elixir. Difficult aphthous ulcers will usually resolve with systemic prednisone or thalidomide.

Dry mouth is common and impairs swallowing, causes halitosis, reduces taste and food enjoyment, induces infection and caries, and may interfere with talking. Providing oral hygiene at least twice per day is helpful and rinsing frequently, chewing gum, using citrus candies, and consuming ice chips are all beneficial interventions. Artificial saliva may also relieve dry mouth, and pilocarpine, 5 mg three times daily, will stimulate salivation.

Sore mouth may be due to oral mucositis, infections, poor dentition, or ill-fitting dentures. Mucositis may be the result of medication or radiation therapy. Conditions like mucositis that involve large surface areas of the oral cavity are often treated with a combination of medications. An example includes acetaminophen, diphenhydramine, tetracycline, dexamethasone, and nystatin that is swished and swallowed or spit every 4 hours.

Dermatological Problems

For reasons that are not entirely clear, HIV patients are commonly afflicted with dermatological disease. Seborrheic dermatitis occurs in up to 80% of patients. Seborrhea will often respond to 1% hydrocortisone and/or topical ketoconazole. Dry skin may be of such severity that it approaches that of ichthyosis and may be accompanied by disabling pruritus. Liberal amounts of skin moisturizers, both water and oilbased, are indicated, in addition to antihistamines like diphenhydramine and hydroxyzine for itching (63,64).

Rashes are common and may be related to drug sensitivity. Any new maculopapular rash that appears up to 7–10 days after the addition of a new medication should

be considered a drug eruption.

Skin infections include boils and carbuncles that may develop into abscesses. Cellulitis is relatively common and usually responds to systemic antibiotics. Fungal dermatoses usually respond to topical antifungals such as clotrimazole (Lotrimin). Disseminated herpes simplex or herpes zoster may be seen and treated with acyclovir, usually by the parenteral route. Molluscum contagiosum, which is due to papillomavirus infection, is common on the face and may be extensive. Regular treatment with cryotherapy, hyfrecation, or topical imiquimod may keep this problematic lesion at bay.

Infestations such as scabies should be suspected when a patient presents with any persistent, atypical rash. In an immunocompromised patient, scabies may develop into what is known as Norwegian or exaggerated, nodular or crusted scabies. It is very contagious because of the increased number of mites carried by each patient. Treatment is more difficult because repeated applications of a scabicide may be necessary to eradicate the infection. Ninety percent of live mites are usually eradicated in ordinary scabies by one application of permethrin or gamma-benzene hexachloride. However, in Norwegian scabies, it may be necessary to continue with repeated applications for up to 6 months.

Wounds may also occur in HIV patients, particularly in advanced disease when pressure ulcers may develop. Management of these conditions includes topical antibiotics and care to improve hygiene and odor. Strong astringents or solutions containing iodine or peroxide are contraindicated because they usually cause damage to normal tissue. Often, when wounds are poorly responsive to conservative measures, they are best managed by covering with protective barrier dressings. For any skin conditions that persist despite treatment, the help of a dermatologist or an ostomy or wound specialist nurse may be required. When appropriate, careful nutritional assessment and treatment may be required for complete healing of these wounds.

Drug Interactions

Some clinically significant drug interactions with medications used for symptom control and HIV antivirals deserve mention. This has been recently reviewed (65). Methadone's metabolism is increased by the following nonnucleoside and protease antivirals: efavirenz, nevirapine, amprenavir, lopinavir/ritonavir, ritonavir, and nelfinavir. Their effects may require an increase in the methadone dose from 35% to 50%. This becomes most important if the above medications are added to a stable methadone regimen, resulting in a loss of analgesia.

The anticonvulsants phenobarbital, phenytoin, and carbamazepine may result in decreased levels of the nonnucleoside and protease inhibitor antivirals that could impair their antiviral effectiveness. Alternative drugs, such as valproic acid and gabapentin, are preferred when antiviral therapy with these agents is ongoing. Midazolam, triazolam, and fentanyl are best avoided due to their impaired metabolism when the same antivirals are being used. Consultation with a knowledgeable pharmacist is recommended when potential interactions exist (64,66).

PSYCHOSOCIAL ISSUES

Fear of abandonment and social isolation are common for individuals living with HIV disease, based on past experience with being judged (67,68). Suboptimal or no provision of health care exists for many of the special populations that are disproportionately affected by HIV because health care providers lack knowledge, or are unaware of specific health care issues in populations or have discomfort in dealing with these groups. Also, some patients feel that many health care providers are discriminatory or hostile and prefer to avoid care because of this. Fear of stigmatization also prevents some individuals from identifying themselves as part of one of these populations (69).

As one example, health care issues in the lesbian, gay, bisexual, and transgender populations are overlooked when health care providers assume the patient is heterosexual. As many as two-thirds of physicians do not ask the sexual orientation of their patients. This is of concern because these patients are at increased risk for suicide, eating disorders, substance misuse, and breast and anal cancer (71). Similar issues arise in the group of patients who have acquired their HIV infection through substance abuse.

Depression, anxiety disorders, psychosis, and substance abuse are major morbidities that these patients suffer (71,72 and 73). A multidisciplinary approach utilizing social workers, psychotherapists and psychiatrists, and community support agencies and groups, can help bring comfort and stability to the lives of those affected. These conditions can lead to homelessness, and nonadherence with appointments and medications, which can all lead to HIV disease progression. Bringing all the help available to those who are willing to receive it can result in improvements in the quality of life, if not overall prognosis.

SPIRITUAL ISSUES

A new diagnosis of any complication of the disease can precipitate a spiritual crisis in an HIV-infected individual. Spiritual crisis or distress occurs when a person is unable to find sources of meaning, hope, love, or peace. Other symptoms of spiritual suffering are disconnection from community, diminished inner capacity to cope, and guilt and shame related to past, negative religious experiences. All clinicians need to understand and identify spiritual suffering (74,75). Religious support and spiritual support are not synonymous. “Spiritual support occurs in the context of an equal human relationship which allows a person to work through his feelings of anger and hopelessness, and achieve a sense of integration and a sense of responsibility. In a secure environment, free of physical suffering, where a patient feels accepted and not alone, it is possible to come to terms with death and view it not simply as giving up out of weakness, but as letting go out of strength” (76).

When a person finds comfort in religious faith, it is important to ensure support is offered in that religion. If a person in spiritual crisis wants religious support by clergy, no one else will do, but it should not be assumed that all community clergy are open and affirming. Many can be judgmental, adding to the patient's guilt and shame; others are not comfortable with death and dying. Palliative care trained clergy understand the complexities of the individual's relationships with religions, and the meaning of self, suffering, and death. Such clergy are important members of the care team and should be asked to see patients in need of help or further assessment for spiritual crisis. Their input can be most helpful for the overall management of the patient.

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79

PALLIATIVE CARE IN THE INTENSIVE CARE UNIT

THOMAS J. PRENDERGAST

Intensive care units (ICUs) combine in one physical location the most desperately ill patients with the most intensive physician and nursing staffing who are trained to use the latest in medical technology. The result is an approach to patient care that has been characterized as “rescue medicine” (1). This term correctly suggests that a primary goal of critical care medicine is to save the lives of patients who would die without its aggressive interventions. The term also carries a negative connotation: In their zeal to save lives, critical care practitioners (intensivists) may undervalue the wishes of the patient, the needs of the family, pain and suffering caused by treatment, and the potential for functional recovery as opposed to mere survival. Since these concerns form the very core of palliative medicine, there is a widespread assumption that critical care medicine is at best indifferent and at worst antithetical to palliative care. For example, one of the major (negative) outcome measures of the SUPPORT study was the presence of a patient in an ICU before death (2).

Accusations of a rescue mentality are anecdotal and difficult to assess (3). We might infer a mindset of rescue medicine when all dying patients receive all therapies, including ineffective cardiopulmonary resuscitation. This was the approach to patients dying in ICUs from their inception in the 1960s through the 1980s. From the late 1980s to the present, however, there has been an astonishing evolution in critical care practice (Table 79-1). In 2001, most ICU deaths follow a considered decision to withhold or to withdraw life-sustaining therapy (4). In the past decade, intensivists have acquired a new responsibility to manage the deaths of patients who do not survive. This is not yet palliative care, but it opens the door to palliative care because it raises the question: How is this newly appreciated responsibility to the dying patient handled, and how well (5)?

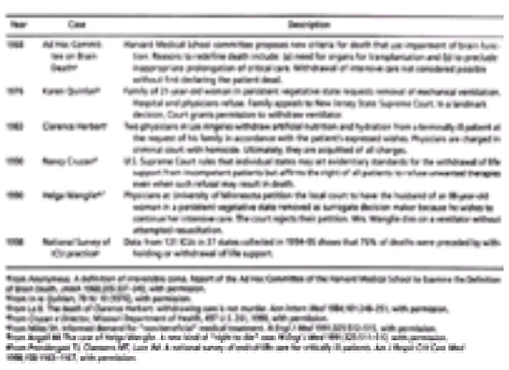

TABLE 79-1. CHANGING MANAGEMENT OF DEATH WITHIN AMERICAN INTENSIVE CARE UNITS (ICUs)

APPROACHES TO PALLIATIVE CARE IN THE INTENSIVE CARE UNIT

Some patients are referred to the ICU for symptom control that cannot easily be provided elsewhere in the hospital. Palliation of symptoms may require intensity of nursing care that is not available on the ward. It may require interventions more comfortably managed in the ICU [e.g., treatment of intractable distress with barbiturate or propofol coma (6)]. The therapeutic goal may be to initiate ICU specific interventions (e.g., vasopressor support or assisted ventilation) to allow time for family to arrive to say goodbye. Instances of specific, circumscribed palliative care are a legitimate, though uncommon, use of critical care resources. For such patients, the ICU is not only an appropriate location but quite likely the best place to die.

Patients admitted for symptom control represent a small minority of ICU admissions. Most patients are admitted to the ICU emergently, under the presumption to treat until more information is available, or because the clinician and patient/surrogate have made a decision to pursue a trial of curative therapy. There is an expectation of recovery or, at least, uncertainty about prognosis. Most patients improve and are discharged. Mortality rates vary from <5% of admissions to some surgical ICUs, to 15% of admissions to general medical ICUs, to 40% or more of admissions to ICUs that treat primarily oncology patients (4,7,8). Age alone does not appear to be an independent predictor of mortality (9). Certain diagnoses place patients at higher risk for death (10,11). Critically ill cancer patients have a particularly poor prognosis, with multiple studies documenting in-hospital mortality rates from 50% to more than 90% in patients who develop critical illness following bone marrow transplant (12). A recent attempt to develop a mortality prediction model specifically for cancer patients identified three variables associated with higher mortality: allogeneic bone marrow transplantation, progression of underlying disease, and poor performance status (7).

Patients admitted to the ICU for curative therapy also may benefit from palliative care. It is uncertain, however, which patients will benefit and when palliation should be emphasized in their course of intensive care. One approach emphasizes symptom control in patients known to be dying. Thus, intensivists may arrive at palliative care through a natural extension of the ICU's core mission to rescue the grievously ill: Treat aggressively for cure until death appears inevitable, then redirect the goals of care to control the patient's symptoms. This model and the accompanying language of transitioning from curative to comfort care have become commonplace in critical care medicine (13,14). The transition approach demonstrates a willingness to acknowledge dying and to attend to the details of patients' deaths. In this sense, it is a significant advance beyond the relentless drive to treat that sometimes has characterized critical care medicine. There are drawbacks to a transition approach, however. To state the obvious, there is more to palliative care than symptom control of the imminently dying. Another problem, one that remains underappreciated outside critical care medicine, is that it is surprisingly difficult to predict who is going to die (15,16).

A transition model of palliative care in the ICU depends on the intensivist's ability to identify a clinical change in individual patients that redirects the goals of care away from curative therapy toward symptom control. Experienced intensivists can accurately predict the short-term mortality of groups of patients; many computer-based mortality prediction models do the same (17). Neither computer-aided decision systems nor expert clinical opinion allows specific identification of the individual patient who will die (16). Data from the SUPPORT study (15) demonstrate that, in most patients, there is no identifiable point when death becomes imminent that allows for a change in direction of care (Table 79-2). These data challenge the assumption that we have advance notice of death. The uncomfortable reality is that a high percentage of ICU patients die but individual ICU patients are difficult to identify as dying. Therefore, if the criterion for palliative care in ICU patients is that providers first recognize that the patient is imminently dying, ICU practice will be deficient in two ways. Many patients will die without the benefit of palliative medicine because they will die unexpectedly. Those who do receive palliative care will receive it very late in their disease course.

Patient population	One day before death (%)	One week before death (%)
All deaths	17	51
Coma	5	27
Congestive heart failure	42	62
Chronic obstructive pulmonary disease	21	41

SUPPORT, Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments.
From Lynn J, Harrell F Jr, Cohn F, et al. Prognoses of seriously ill hospitalized patients on the days before death: implications for patient care and public policy. *New Horiz* 1997;5:56–61, with permission.

TABLE 79-2. MEDIAN PREDICTED 2-MONTH MORTALITY IN SUPPORT

Despite an emerging consensus that palliative care can coexist in parallel to aggressive critical care, many clinicians in and out of ICUs strongly support the concept of a transition to palliative care. There are many reasons for the persistence of this approach. A few patients do have an abrupt change in their clinical course that significantly changes their prognosis (e.g., the elderly patient with lung cancer who has a myocardial infarction that precipitates cardiogenic shock). Predicted survival may drop precipitously with additional organ dysfunction, and appreciation of this change may facilitate a decision to limit therapy. In other patients, the decision to change the direction of therapy is based on nonprognostic factors, such as suffering, quality of life, or comorbid illnesses, that suggest a high likelihood of recurrent hospitalization or death despite the possibility of short-term recovery (18). That same patient, now hemodynamically stable but with severe, permanent left ventricular dysfunction, may face a degree of debilitation that he and his family find unacceptable. Sometimes, clinicians and families frame the facts to suit their need for explanations in a way that creates transitions (19). Perhaps this patient's quality of life will be no different after his myocardial infarction but the event reshaped the patient and family's thinking toward acceptance of his mortality.

Finally, the transition model permits separation of the curative and palliative roles. To the extent that this separation allows the intensivist to withdraw from involvement as death approaches, it may represent a strategy to cope with feelings of helplessness, failure, and grief (20). The alternative, to assert that all patients at high risk of dying need palliative care, asks the intensivist simultaneously to be an advocate of rescue and palliative medicine (15,21). To assume both these roles is to move far beyond the transition model.

ADAPTING PALLIATIVE CARE TO THE INTENSIVE CARE UNIT

Palliative care in or out of the ICU starts with adequate symptom control. Symptom control is essential because pain and suffering without purpose are destructive, because untreated pain may adversely affect outcomes (22,23), and because unrelieved pain and suffering interfere with the patient's ability to address important life issues that may be brought to closure before death. Palliative medicine promises more than symptom control, however. It emphasizes the possibility of growth at the end of life. Palliative care means acknowledging and addressing psychological suffering (depression, anxiety), existential suffering (estrangement, alienation, lost opportunities, the meaning of one's life), and spiritual suffering (Why am I dying?) (24). This ideal of palliative care depends upon a predictable disease course that allows time to plan and a patient who is alert enough to speak for himself and to participate in discussions of both medical planning and personal growth with a provider who has a relationship with the patient and, preferably, has known the patient and the family over time. Critical care medicine violates this model in almost every respect (Table 79-3) (25).

The *raison d'être* of critical care medicine is to push the limits of what medicine can accomplish. Success is measured in lives saved. Lives lost may be accounted as failure. The importance of the quality of death is not part of the culture.[a]
ICUs are different from other hospital locations in that the organizing principle is the acuity of illness. Geographically and organizationally, the focus of care is on technology and interventions rather than on interpersonal relations.[b]
The ICU environment is characterized by acute illnesses with unpredictable outcomes.[c] Clinical status may change rapidly, necessitating rapid decision making about life and death issues.
Patients rarely have a preexisting relationship with their providers. Most patients who die are too ill to participate in discussions of their needs and wishes. Communications with family and surrogates are strained by lack of prior relationships, time-pressured decision making, and uncertainty of prognosis.[d]
Critical care education has emphasized the core mission of aggressive treatment of the acutely ill or injured, with little attention to palliative medicine. As a result, there is a lack of knowledge of palliative medicine.

[a]From Gilligan T, Raffin TA. Physician virtues and communicating with patients. *New Horiz* 1997;5:8–14, with permission.
[b]From Nelson JE, Meier DE. Palliative care in the intensive care unit: part I. *J Intens Care Med* 1999;14:138, with permission.
[c]From Lynn J, Harrell F Jr, Cohn F, et al. Prognoses of seriously ill hospitalized patients on the days before death: implications for patient care and public policy. *New Horiz* 1997;5:56–61, with permission.
[d]From Pennebaker TJ. Resolving conflicts surrounding end-of-life care. *New Horiz* 1997;5:67–71, with permission.

TABLE 79-3. SOME OBSTACLES TO PALLIATIVE CARE IN THE INTENSIVE CARE UNIT (ICU)

Some of the barriers to palliative care listed in Table 79-3 actually contribute to the success of critical care medicine. An emphasis on technology, and expert providers willing to push its limits, are desirable if they help the desperately ill and injured. Other barriers seem inevitable if less desirable. In an environment dedicated to treating the sickest patients, prognostic uncertainty dictates that some patients will die under aggressive therapy in order successfully to treat those who survive. This is neither a mistake nor necessarily a failure but an expected consequence of not knowing who will respond to treatment (21). The nature of critical illness is that clinical situations change rapidly and decisions must be made quickly. Pervasive prognostic uncertainty, pressure to make decisions, and significant mortality seem inescapably part of the ICU environment. Some barriers in Table 79-3 are cultural and, therefore, subject to change. Struggling to save lives is fully consistent with acknowledging that the quality of death can be as important as the quality of life (26). To teach the importance of interpersonal relations and communications skills need not devalue the technical and scientific accomplishments that distinguish modern critical care. Technology does not imply dehumanization; intensivists can be full participants in the human stories being played out under their care.

There are key elements of palliative care that are adaptable to the ICU in a way that improves the care of patients while respecting the critical care provider's appropriate role as advocate for the desperately ill. These features of palliative medicine are not inconsistent with good ICU practice. They are increasingly seen to define good ICU practice (13,21,27,28 and 29). The internist or oncologist whose patient is admitted to the ICU may reasonably expect this degree of expertise from their ICU staff, if not now, at least as a goal to be reached in the near future.

First, as mentioned, it is absolutely essential that adequate attention be paid to symptom control. There are very few situations in which attention to the physical and psychological needs of patients conflicts with curative treatment. Palliative care can teach the intensivist about good symptom management.

A second aspect of palliative care applicable to the ICU is to recognize that each individual patient lives within a web of human relationships. To care for a critically ill patient is to have a relationship not only with the patient but also with all those people to whom the patient is connected. Regardless of the caregiver's interest or willingness to explore those relationships, he or she cannot escape the complex and frequently difficult communications environment that those relationships create. The ability to communicate effectively with groups of people is absolutely essential to the intensivist. Since uncertainty about prognosis is pervasive and colors everything else that occurs in the ICU, a communication strategy that diffuses the power of uncertainty by acknowledging it directly facilitates good ICU care while opening the door to good palliative care.

Third, a fundamental principle of palliative care is acceptance of impending death, by the patient, by loved ones, and by the health care provider. In the ICU, the unexpected nature of illness or injury combined with prognostic uncertainty leads to common self-protective strategies. In their hope of recovery, family members may deny the possibility of death while physicians may avoid discussion of death. The approach from palliative care means acknowledging the possibility of death in an ongoing discussion with the family and, when appropriate, moving to limit life-sustaining treatments. It is in the area of withdrawal of life support that intensivists have most clearly changed their practice and where the most concrete recommendations can be offered.

PAIN AND SYMPTOM CONTROL IN THE INTENSIVE CARE UNIT: GENERAL PRINCIPLES

There are multiple reasons for patients to experience pain, anxiety, dyspnea, and other distressing symptoms during treatment in the ICU. Operative surgical procedures, bedside instrumentation, placement and maintenance of an endotracheal tube, including endotracheal suctioning, and prolonged immobilization, in addition to the trauma or serious illness that warranted hospitalization in the first place, all may cause significant physical and psychological symptoms (30,31). Patients

report significant distress associated with pain that may manifest as anxiety or agitation (32). Hunger, thirst, and disruption of sleep were reported as moderate or severe by more than 50% of ICU patients in a recent survey (33). The act of weaning patients from mechanical ventilation may be associated with significant anxiety even in patients who are clinically improving (34). The overall symptom burden may be particularly high in dying patients (35).

Despite the apparent prevalence of pain and other symptoms, rigorous research into prevalence and control of symptoms has been scarce. In part, this lack of research reflects the difficulty of symptom assessment in ICU patients. Critically ill patients frequently have altered cognition, they may be heavily sedated, and a significant proportion are endotracheally intubated, which renders them speechless. Although there are symptom assessment tools that can assist providers in obtaining information in many patients (36,37), including intubated and dying patients (33), these tools are time and labor intensive, and have not generally been tested for both reliability and validity (38,39). In the routine practice of critical care medicine, symptom assessment has been subjective and poorly standardized (40).

The most basic principle in the assessment of pain is that pain is irreducibly subjective (36). Therefore, the best indicator of pain is the patient's own report. Patients who can report their pain should be treated accordingly, even though their cognition may be altered by illness or medication, and the stress of critical illness may significantly change their ability to cope with or to describe pain. Appropriate treatment always requires a careful pain history, particularly a history of chronic opioid use, to dose analgesics correctly. Instruments available for patients who can communicate range from a simple linear scale to quantify the pain, to more intricate inventories of psychological states such as the McGill Pain Questionnaire (41). Visual analog scales require less cognitive processing than visual descriptors or numerical rating scales but do require that the patient be able to see (36). None of these scales has been validated in critically ill patients.

Patients who cannot describe pain may manifest it as “agitation.” Agitation is not a diagnosis but a description of excessive or inappropriate motor activity. Despite the difficulty of identifying a specific etiology, a diagnostic review of the agitated patient is essential before instituting therapy. Anxiety, fear, frustration with inability to communicate, pain, delirium, dyspnea, and ventilator dyssynchrony all may manifest as agitation. Failure to search for an etiology may lead to inappropriate treatment. To treat pain with sedatives that have no analgesic properties may require excessive sedation to the point of general anesthesia. Delirium may be exacerbated by opioids or benzodiazepines and is best treated with haloperidol.

In the 50% or more of ICU patients who cannot report their subjective experience, assessment is particularly dependent on careful physical examination for potential sources of pain, such as early decubiti, pressure points, intravenous lines, surgical wounds, traumatic fractures, and constricting bandages or restraints. Assessment of the nonverbal patient also depends on observation of nonspecific physiological data, such as changes in blood pressure and heart rate, tearing or diaphoresis, along with a subjective assessment by the provider of the patient's appearance and how the patient responds to specific treatments such as turning, positioning, and suctioning (36,42). Observational methods that do not elicit information directly from the patient lack sensitivity and specificity (33,40). Family members may help interpret nonverbal information in such patients, although the validity of such surrogate interpretations is unknown.

Virtually all ICU patients require sedation, analgesia, or both to protect them and facilitate their treatment (43). To administer sedating agents presupposes a therapeutic goal and a way to determine when that goal has been reached. These goals are sometimes poorly defined, the assessments may be made subjectively, and documentation of both is frequently poor. A recent systematic review of sedation scoring systems (38) identified 25 sedation instruments, of which only four (one pediatric scale) had been tested for both reliability and validity. The oldest and most widely used scale in adult ICU patients is the Ramsay Scale (44). In many institutions, this has been superseded by instruments that discriminate better among levels of agitation (Table 79-4). A first step in improving sedation practice is to standardize assessment of therapeutic goals and patient assessment using one of these instruments. Systematic assessment can be combined with therapeutic algorithms to perform continuous quality improvement (45). Nonpharmacological strategies to manage agitation may be underutilized (46,47).

Rating	Ramsay scale[a]	Sedation-agitation scale[b]	Motor-activity assessment[c]
0	NA	Minimal or no response to noxious stimuli	Unresponsive to noxious stimuli
1	Asleep, no response to light glabellar tap	Arousable by physical stimuli but does not follow commands	Responsive only to noxious stimuli
2	Asleep, sluggish response to light glabellar tap	Difficult to arouse but follows simple commands	Responsive to touch or name
3	Asleep, brisk response to light glabellar tap	Calm, awakens easily, follows commands	Calm and cooperative
4	Awake, responds to commands only	Anxious or mildly agitated, but calms to verbal instructions	Restless and cooperative
5	Awake, cooperative, oriented and tranquil	Very agitated, does not calm with verbal instructions	Agitated
6	Awake, anxious, agitated or both	Dangerously agitated, uncooperative	Dangerously agitated, uncooperative

NA, not applicable.
Numerical coding modified to show parallel elements among the three scales.
[a]From Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with alphaxalone-alphadolone. *BMJ* 1974;2:656–659, with permission.
[b]From Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. *Crit Care Med* 1999;27:1325–1329, with permission.
[c]From Devlin JW, Boleski G, Mlynarek M, et al. Motor Activity Assessment Scale: a valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. *Crit Care Med* 1999;27:1271–1275, with permission.

TABLE 79-4. QUANTITATIVE ASSESSMENT OF SEDATION IN CRITICAL CARE

Current Practice

Most of the data regarding symptom control are found in studies of pharmacological management of pain and agitation. There is a paucity of data on nausea, dyspnea, sleep deprivation, etc. Studies of pain management in the ICU suggest systematic undertreatment. The SUPPORT study (2) is a major reference point for the management of pain in severely ill, hospitalized patients, half of whom were treated in ICUs during their hospitalizations. Twenty-two percent of patients interviewed in the second week of the SUPPORT study reported that they had had “moderate or severe pain all, most, or half the time.” Family members of patients who died reported that their loved ones had been in moderate or severe pain 50% of the time. Puntillo reported a series of 24 primarily surgical ICU patients in which 63% of patients reported moderate to severe pain (48). Whipple et al. investigated the different perceptions of physicians, nurses, and 17 ICU patients admitted to the ICU after traumatic injury (49): 95% of house staff and 81% of nurses reported the patients received adequate pain control but 74% of patients reported significant pain (27% moderate and 47% severe). The conclusion seems inescapable: Intensivists systematically undertreat pain.

On the other hand, a number of recent papers have raised questions about systematic oversedation. Kress and colleagues reported the results of a randomized controlled trial in 128 medical ICU patients (50). In the intervention group, sedative infusions were interrupted each morning until the patients were awake or uncomfortable; in the control group, the infusions were not interrupted routinely but at the discretion of the ICU clinicians. The investigators found a shorter duration of mechanical ventilation and shorter ICU length of stay in the intervention group, along with fewer diagnostic studies to assess altered mental status. No measure of patient distress or satisfaction was reported in the original paper. The authors have subsequently published in abstract form a summary of patient interviews that does not reveal any difference in psychological wellbeing, depression, or posttraumatic stress disorder between intervention and control patients (51). Only one patient of twelve recalled awakening from sedation; that patient was a control subject. These data suggest that, in a medical ICU, the current standard of practice sedates mechanically ventilated patients so heavily that it may prolong their ICU stay.

It is not yet clear how to reconcile these findings with data that pain is undertreated. Sedation may be given excessively while analgesics are underdosed. In particular, continuous infusion of sedatives and analgesics may prolong mechanical ventilation but the constant levels so achieved may not suffice for procedural pain from suctioning, turning, and other aspects of ICU care that patients report are uncomfortable (52). Given the paucity of data on patient distress or satisfaction, it may be that adequate symptom control requires medication that itself prolongs ICU treatment (33).

There are even fewer data about the management of pain and sedation in ICU patients at the end of life. This clinical context is very specific: The majority of patients who die in ICUs have life support withheld or withdrawn. The usual considerations of balancing adequate sedation with hemodynamic stability or avoiding prolongation of mechanical ventilation are no longer issues. There may be new considerations. Some patients may want to remain alert as long as possible to be able to communicate with their families. Some providers may worry about administering large amounts of opioids or sedatives to a patient who will die soon afterwards, for fear that such practice blurs the line between withdrawal of life support and active euthanasia.

Two studies speak to this question. In 1988–89, Wilson and colleagues retrospectively reviewed all patients over 1 year who had life support withheld or withdrawn at San Francisco General Hospital (53). They randomly selected an equivalent number (N = 22) of patients from their affiliated University Hospital. Seventy-five percent (33/44) of patients received sedation or analgesics or both, at doses that were significantly increased from baseline once the decision was made to withdraw life support. All the patients died. The minority who did not receive sedation were deeply comatose and died faster that those who did receive additional medication. The authors concluded that administration of opioids and sedatives was common in the withdrawal of life support from ICU patients and did not appear to hasten death. The latter conclusion was seriously weakened by significant clinical differences between the two patient groups.

Hall and Rocker reviewed charts from 174 consecutive patients who died over a 1-year period in 1996–97 (54). Seventy-nine percent (138/174) had life support withheld or withdrawn, while 21% (36/174) had aggressive therapy continued up to the time of death. Doses of morphine and lorazepam were fivefold higher in patients from whom life support was withdrawn, and most of this increase occurred in the 4 hours prior to death. Of interest, neuromuscular blocking agents (NMB) were

administered in the final 12 hours of life to 25 patients, of whom 17 had it started in the last 12 hours of life. In 20% (5/25), there was a single dose to facilitate endotracheal intubation. Nine patients had a NMB infusion at the time of death, 5 of whom had life support (but not mechanical ventilation) withdrawn. Sixteen percent (4/25) of patients receiving NMB were receiving intermittent sedation/analgesia but not continuous infusions.

These and other studies show that the range of opioid doses necessary to control acute pain or dyspnea is very wide; large doses may be necessary. However, the milligram dose is much less relevant than careful administration. It is entirely appropriate to give large amounts provided that these doses are carefully titrated to specific effects. In rare cases, it may only be possible to control symptoms with doses that hasten death. Provided that the intended effect is relief of suffering and the doses are carefully titrated to that effect, there is broad consensus in bioethics and the law that ameliorating symptoms is not euthanasia, i.e., not the deliberate administration of drugs with the intent to terminate the patient's life (55,56). One of the most egregious failings in end-of-life care is the systematic failure adequately to treat pain and dyspnea, based on a misunderstanding of this distinction (57).

Specific Recommendations

There is a modest amount of data describing current practice in pain and symptom management in ICUs. There is much less data to clarify how effective this therapy is in order to make specific treatment recommendations. A recent, systematic review of randomized, controlled trials comparing at least two different agents for the sedation of ICU patients found a discordance between the prevalence of use of sedatives (multiple reviews identified between 11 and 23 different agents used in the United States and United Kingdom) and a paucity of data (58). Of 49 studies identified, only 32 met minimal criteria for adequacy of study design, and of these 32, 20 compared propofol to midazolam. This literature is largely driven by pharmaceutical companies seeking data to support the use of specific medications. If the measure of efficacy is patient/family satisfaction, then there is little information to guide practice. Any recommendations are at the level of consensus guidelines and expert opinion (40).

First, and logically necessary to any improvement in practice, is that intensivists need to place a higher emphasis on specific symptom control. The first step is to incorporate systematic symptom assessment into their routine practice (33).

Second, intensivists must be expert in the use of a fairly small number of analgesic and sedative agents. Expertise includes understanding the pharmacokinetics and metabolism of these agents. With opioids and some benzodiazepines, the plasma elimination half-life is a poor measure of clinical effect because the onset of activity and duration of effect are more closely tied to distribution and redistribution of the drug into and out of the central nervous system. One must also understand how these properties are altered in the setting of advanced age (59) and critical illness (60,61). The presence of increased extravascular water increases the volume of distribution of many drugs. Changes in plasma protein levels will affect protein binding and may increase concentration of free drug. Impairment of hepatic and renal function affects metabolism and clearance. Agents (midazolam) that undergo oxidation-reduction are affected by age, disease states, such as cirrhosis, and competing pharmaceuticals far more than drugs (lorazepam) that undergo glucuronidation (62). Pharmacokinetic data are obtained in studies of healthy volunteers and may not be applicable to critically ill patients (Table 79-5 and Table 79-6).

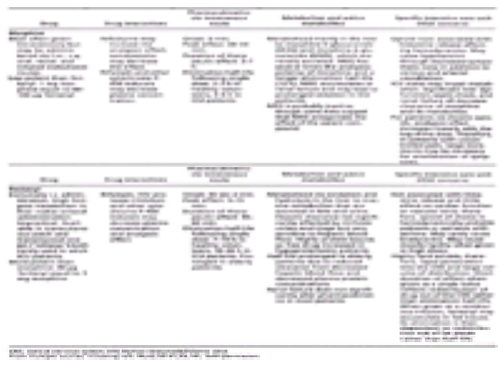

TABLE 79-5. OPIOID ANALGESICS COMMONLY USED IN INTENSIVE CARE

TABLE 79-6. AGENTS COMMONLY USED FOR SEDATION IN INTENSIVE CARE

As a practical matter, intravenous administration is preferred in the ICU. Virtually all patients have intravenous access, and many have central venous access that permits administration of agents that are irritating when given by peripheral vein. Intravenous administration reduces the variability in absorption seen in enteral or subcutaneous routes. Enteral administration is complicated in the ICU patient by impaired gastric emptying, decreased intestinal motility, nasogastric suctioning, diminished intestinal blood flow either due to illness or administration of vasoactive agents, and reduced absorptive surface area (63). Because the exact dose of analgesics or sedatives is less important than titrating the dose to clinical effect, some agents that are well-absorbed enterally (lorazepam, diazepam, and haloperidol) can be given via that route. Most medications are dosed by continuous infusion, however. In the case of pain, it is essential to control the pain adequately with bolus dosing before relying on a continuous infusion.

Opioids have a variety of beneficial effects in ICU patients (Table 79-5). Opioids have potent analgesic properties but are only mild sedatives and do not have specific anxiolytic effects apart from those consequent to reduced pain. Opioids may cause euphoria but do not produce amnesia. They are potent antitussives that depress upper airway and tracheal reflexes, facilitating tolerance of an endotracheal tube without coughing or fighting against the ventilator.

Opioids are potent respiratory depressants. They produce dose-dependent inhibition of respiratory rate, tidal volume, minute ventilation, and ventilatory response to CO_2 (64). This effect is potentiated by concomitant administration of benzodiazepines (65). Chronic administration of opioids is associated with tolerance to the respiratory depressant effects of opioids but this process takes many months (66). Therefore, ICU patients typically are sensitive to respiratory depression though it is rarely a pressing concern in patients who are intubated. At equianalgesic doses, no opioid is more or less likely than another to produce respiratory depression. Opioids cause urinary retention, decreased intestinal motility, and delayed gastric emptying. At high doses, they may cause adynamic ileus. Tolerance does not develop to constipation. Opioids may cause nausea through direct stimulation of the chemoreceptor trigger zone.

Benzodiazepines are safe and inexpensive medications that have become the drugs of choice for sedation in intensive care patients (Table 79-6). Benzodiazepines have potent anxiolytic and amnestic properties and are mild hypnotics. At higher doses, they are effective at preventing and treating seizures. They may have some antiemetic effects but this is not a potent property. They have no intrinsic analgesic properties and so are commonly given with an opioid for better control of symptoms at lower doses. Benzodiazepines do not have significant hemodynamic effects at usual doses though midazolam may precipitate hypotension in some patients. They do have mild central respiratory depressant effects that are synergistic with opioids (65). Midazolam has the most effect on the ventilatory response to CO_2 and can cause apnea when given at higher doses (induction of anesthesia) or in susceptible (principally elderly) patients. Lorazepam and, especially, diazepam cause venous irritation when given intravenously. Midazolam is prepared as a water-soluble solution and does not cause phlebitis.

Propofol is a potent intravenous hypnotic and anesthetic that is increasingly used in the ICU for short-term, titratable sedation (Table 79-6). Propofol causes a dosedependent fall in blood pressure through both direct depression of cardiac output and peripheral vasodilation. This effect is much more pronounced when given as

a bolus than when given as a continuous infusion. The hypotensive effect is augmented by concomitant opioid administration. Propofol is a respiratory depressant that causes dose-dependent depression of tidal volumes, minute ventilation, and ventilatory response to carbon dioxide. Apnea is common after induction of anesthesia with propofol. Propofol has demonstrated antiemetic properties during maintenance of anesthesia (67) to reduce postoperative nausea and vomiting after standard anesthesia (68) and to reduce chemotherapy-induced emesis (69,70). Haloperidol is a high-potency, nonspecific dopamine antagonist that is the agent of choice for management of delirium and psychosis in intensive care (Table 79-6) (71).

COMMUNICATIONS: GENERAL PRINCIPLES AND CURRENT PRACTICE

Multiple aspects of critical illness make the ICU a difficult communications environment. Most ICU patients were not terminally ill and many were healthy before an unexpected catastrophic illness or injury. The ability to predict outcome, though excellent across populations, is very limited in individuals (16). The threat of death or significant disability is real but intensivists rarely have an established relationship with their patients. In many cases, they never have the chance to speak to them because most patients are unable to participate in their treatment decisions (18,72,73). Patients admitted to ICUs rarely have completed advance directives (74,75), and the advance directives that are written are frequently too general to be helpful (76) or contain internal inconsistencies (5).

Family members of ICU patients confront difficult choices in a complex and unfamiliar environment. Surrogate decision makers are called on to make decisions about continuing or withdrawing life support, despite the fact that correlation between the patient preferences and their relatives' predictions of those preferences is poor (77,78). When asked about their needs, family members emphasize communication of information (Table 79-7). Despite the importance to families of clear communication, this does not appear to be a strength of critical care practice. Fifty-four percent of families of ICU patients in one study had significant misunderstandings of diagnosis, treatment, or prognosis (79). This lack of comprehension occurred despite the ability of physicians to identify family members who did not understand and despite a positive correlation between understanding and the amount of time physicians spent with the family. Of interest, for the readership of a textbook of supportive oncology, there was a high correlation between family misunderstanding and referral from hematology or oncology.

To have questions answered honestly
To know specific facts about what is wrong with the patient
To know the prognosis for recovery
To be called at home about changes in the patient's status
To receive information from the physician (at least) once daily
To receive information in understandable language
To believe that hospital personnel care about the patient
To be assured of the patient's comfort
To be comforted
To express emotions
To find meaning in the death of their loved one
To be fed, hydrated, and rested

Adapted from refs. 27,28,89,90,140, with permission.

TABLE 79-7. A DOZEN NEEDS OF THE FAMILY IN THE SETTING OF CRITICAL ILLNESS

In addition to the lack of skill or unwillingness to convey medical information to family members, intensivists may not listen carefully to the patient's and family's needs. Twenty-five percent of bereaved families in one study believed that neither the patient nor the family was part of the discussion about end-of-life decisions (80). Only 29% of patients in SUPPORT who preferred palliative care thought that the care they received was consistent with their wishes (81), and they reported low rates of discussions with physicians about their prognoses and preferences. In a survey of American Thoracic Society members, 34% of intensivists reported continuing therapy that the patient/surrogate requested be discontinued, and 82% of physicians made unilateral decisions to withdraw therapy, often without the knowledge or consent of the patient/surrogate and sometimes despite their objections (82).

Prognostic uncertainty and strained communications around unpredictable problems create fertile ground for disagreement. Disputes about management are not the exception in the ICU; they are ubiquitous—an integral part of the critical care environment (83,84 and 85). It remains unknown how many physician-family disputes are the result of ineffective communications by physicians. Disputes arise as often among physicians as between physicians and families (18). Despite the common assumption that nurses are more effective communicators than physicians, there is evidence that skills are not different between these groups (86).

Recommendations for Practice

Patients and families express needs for better communications with their physicians. In the ICU, this means that intensivists are called to build relationships, facilitate decision-making, and negotiate disagreements, in addition to learning how to deliver bad news (87). There are two problems with making concrete recommendations for improved practice in this area (88). First, much of the literature is based on expert opinion and is not grounded in empirical research. Second, the research that exists is written largely from the perspective of the caregiver. Perhaps the most important recent development in this area is the appearance of many attempts to elucidate the patient's and family's perspective (32,79,89,90 and 91). A first step toward improved ICU communication is to acknowledge this literature and, thereby, the importance of illness (i.e., the patient/family's subjective experience of their biomedical disease) (90). A second step is to eradicate the implicit and false assumption that communication with patients and families is a skill that every nurse and physician possesses. In fact, there are approaches to patients that are demonstrably more and less effective at facilitating communication (92,93). These approaches are skills that can be learned (94,95,96 and 97). Acknowledging the need for training may be difficult because physicians tend to believe that they are communicating effectively despite evidence that they are not (98,99).

A second development that gives hope for improved communications in the ICU is empirical research into the extraordinary complexity of treatment discussions, particularly those surrounding withholding and withdrawal of lifesustaining therapies. Recent work confirms that the act of withdrawing life-sustaining therapy from a patient is not the result of a single decision but emerges from the process of ongoing care (100,101 and 102). One implication of this work is that intensivists must recognize not only how important family discussions are to families but also how essential they are to the practicing intensivist (103,104).

The astute intensivist sees in the critical care setting opportunities for creating relationships. One rationale for advance directives is an underlying mistrust of physicians (105,106), and one task in discussing end-of-life care is to overcome that mistrust. In the outpatient setting, it takes a special effort on the part of physicians to establish a relationship that allows meaningful advance care planning. Insofar as ICU care is an emergent, unexpected event, the lack of previous relationship may open an opportunity to bypass mistrust. The clinician and the patient are brought together under extraordinary circumstances. There is often a sense of shared goals. Family and physician both seek the best possible care for the patient leading to recovery, if possible. Most want to avoid overtreatment if recovery is not possible. These shared goals form the basis of a natural alliance that the skilled intensivist can build upon to facilitate communications (106).

Preferences for end-of-life care are not fixed qualities that a patient discovers upon reflection. A decision to pursue risky therapy or to forego further intensive care is not made in the abstract. Preferences for care emerge from a process of discussion and feedback within the network of the patient's most important relationships (100). Such decisions are inevitably embedded within a social context. The ICU environment can make this communication easier, not harder, because there is a natural iterative pattern in meeting with a family through the course of a critical illness. The ability to meet repetitively over time provides an opportunity to build trust. These meetings also create a new social context in which the intensivist plays an important role in the ongoing development of preferences for care. These conversations hold the key to end-of-life decision-making in the ICU (102,105,107).

WITHHOLDING AND WITHDRAWAL OF LIFE SUPPORT: GENERAL PRINCIPLES

The majority of patients who die in North American ICUs now die following a considered decision to withhold or withdraw some form of life-sustaining therapy (4,54,108). This represents a recent, secular trend in North America toward more active management of dying ICU patients (18,109,110) as well as a dramatic change from earlier practice (Table 79-1). There is a broad ethical and legal consensus that withdrawal of life-sustaining therapy is appropriate in many circumstances (55,56,111,112,113,114 and 115). Nonetheless, there remains significant variation in practice (Fig. 79-1). The reasons for this variation are not clear, but it does not appear to be associated with size, type of ICU, or the number of admissions (4). The attending physician's status may be a relevant factor (116).

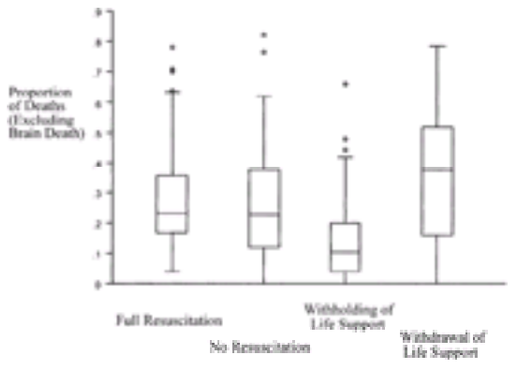

FIGURE 79-1. Variation in the practice of withholding and withdrawal of life support among 131 American intensive care units. Actual mean percentages (range) are as follows: full support, including cardiopulmonary resuscitation (CPR), 26% (4–79); do not resuscitate (DNR), 24% (0–83); withholding, 14% (0–67); withdrawal, 36% (0–79). (From Prendergast TJ, Claessens MT, Luce JM. A national study of end-of-life care for critically ill patients. *Am J Respir Crit Care Med* 1998;158:1163–1167, with permission.)

There is a great deal of descriptive research on the process of withdrawal of life-sustaining therapy (53,54,73,76,117,118 and 119). Any therapy that sustains life can be withheld or withdrawn. The most common therapies are, in the approximate order of frequency with which they are withdrawn: blood products, hemodialysis, vasopressors, mechanical ventilation, total parenteral nutrition, antibiotics, intravenous fluids, and enteral feedings. The majority of physicians opt to withdraw therapies in a sequence; the therapies most likely to be withdrawn first are those that are scarce, expensive, or invasive. Many physicians will first withdraw the therapies with which they are most familiar. There are many suggested algorithms for withdrawing different technologies (120,121,122 and 123). These recommendations are based on expert opinion. Few studies report patient comfort, family satisfaction, or the experience of caregivers on which to base a recommendation (124).

Patients and surrogates, or clinicians, or both, may pursue intensive care too long before acknowledging the appropriateness of limiting therapy. Patients and physicians usually move to limit therapy when hope for recovery is outweighed by the burdens of continuing treatment. Most disagreements about continuing therapy are not about the merits of treatment in the face of incontrovertible evidence that it has failed. Physicians and families most often disagree about how to value a small chance of improvement, or how to weigh the continuing burdens of treatment, be they physical, emotional, financial, or in loss of dignity. The difficulty in making such judgments in the face of inadequate information naturally leads to disagreements. Most often, these disagreements are handled through an intuitive process of negotiation. The parties agree on a time-limited trial of therapy, followed by review and withdrawal if the patient has not improved. In a small percentage of cases, the perspectives of the patient/surrogate and the treating physicians are difficult to reconcile, and one party may insist on treatment against the strong recommendation of the other. Many physicians attempt to apply the concept of medical futility to such requests to reassert the prerogative to make the decision they favor (125). Because there is no consensus definition of medical futility, this approach should be avoided. The Council on Ethical and Judicial Affairs of the American Medical Association has recently suggested an alternative, procedural approach based upon the experience of researchers in Denver and Houston (126). It is important to recognize that while each side—the medical community and patient advocates— accuses the other of demanding overtreatment, the evidence suggests that physicians and families are about equally responsible (85).

Suggested Protocol for Withdrawal of Life Support

A. *Clarify the decision.* Establish consensus on withdrawal among the medical team members. Responsibility to proceed with withdrawal remains with the patient/surrogate in consultation with the attending physician, but it is essential to know if there are significant concerns among consulting physicians, nursing, respiratory care, or other members of the critical care team. Members of the team may reach the conclusion that therapy should be discontinued at different times. Unanimity is not to be expected in all cases. Common areas of disagreement include misunderstandings of legal responsibility and liability, disputes over prognosis, and a tendency to focus on survival to ICU discharge that neglects the patient's long-term survival. If disagreements among the critical care team cannot be resolved in advance of the decision, their concerns must be noted as a sign of professional respect.

   Identify the appropriate decision maker, patient, or surrogate. Establish consensus on proceeding among patient/family. As with the medical team, unanimity is the goal but is not to be expected in all cases. All critical care providers should hone their skills in understanding the dynamics of family discussions. In particular, speculation as to motivations of family members should be discouraged while encouraging an appreciation for the difficulty of allowing a loved one to die. Providers should be particularly sensitive to framing discussions that suggest that the family's or surrogate's decision is responsible for the patient's death. In almost every case, this is simply inaccurate: The decision is made in accordance with the patient's wishes.

   Document the discussion as well as the plan in the medical record.

B. *Identify patient/family goals.* Nearly all patients who have life support withdrawn in a critical care setting die soon thereafter. This is usually not in doubt but should be made clear if it is not already.

   Some patients and most families ask for comfort above all else. Ensuring comfort often comes at the cost of diminished level of consciousness. Occasional patients will want to visit with loved ones and are prepared to tolerate some physical distress in order to be present to them. Others simply want to be asleep. In order to provide excellent care, it is essential to establish with the patient or surrogate the primary treatment goals following the withdrawal of life support.

C. *Review the process with family, and patient, if awake* .Emphasize comfort consistent with patient goals (above). Describe the plan to deal with any complications of withdrawal. Do not make promises that you cannot keep, e.g., adequate analgesia and sedation may not prevent some gasping or gurgling of secretions. Reassure the patient/family that you have a plan to treat these signs should they appear.

   Address length of survival. Family members frequently ask how long a patient will live after the withdrawal of life support. They deserve an answer, even if it is only an educated guess. In most cases, it is possible to put a patient's prognosis into categories of minutes to hours, hours to days, days or more. Often, the clinician can be much more specific. Of course, there will always be patients who will surprise their caregivers and prove their predictions wrong. They are few, and it is better to be helpful to the vast majority of families and risk the occasional mistake than to refuse to answer a legitimate question.

D. *Create a calm environment.* To the extent possible, isolate the patient from the noise and activity of the ICU. Provide a private room or draw curtains. Liberalize visiting rules. Allow children at the discretion of the patient/family.

   Any technology that is not providing comfort to the patient should be removed. Remove lines and tubes, turn monitors off, disable alarms, discontinue routine measurement of vital signs. Discretion will be needed with urinary drainage catheters because removal may be uncomfortable and obstruction may ensue. At least one intravenous catheter should remain in place for the administration of sedatives and analgesics.

E. *Principles of symptom management in withdrawal:*
   1. A physician should be at the bedside at the start of a process of withdrawal, regardless of the therapy withdrawn. Most decisions to allow a patient to die are distressing for the family and fraught with secondguessing. The continued presence of the attending physician at the time of withdrawal makes a strong statement to the family of nonabandonment in the face of death, of continued involvement, while dying, to ensure comfort, and of the importance to the medical team and, by inference, to the hospital of the importance of a good death. The absence of the attending physician may send the opposite message. The presence of the attending physician is also valuable to any trainees or students who may have participated in the patient's care. Obviously, a clinician should be available to assess and to respond to significant changes in the patient's status as therapy is withdrawn.
   2. Medications must be immediately available at the bedside.
   3. Administration of medications should be guided by anticipatory dosing, particularly when making changes that are highly likely to cause distress such as discontinuation of assisted ventilation or removal of an endotracheal tube.
   4. Medications should be titrated to effect. The effect is comfort, not apnea. There is no *a priori* maximal dose. It is difficult to assess discomfort in comatose patients. If a patient appears uncomfortable, it is acceptable practice to administer analgesic and/or sedatives under the assumption that he may experience something. Family suffering in the presence of an uncomfortable patient may be palpable. It is acceptable practice to administer medication to make the patient appear more comfortable provided that the intent is not to hasten death.
   5. Continuous infusion is preferable to bolus dosing although a bolus is often appropriate prior to increasing a continuous infusion dose, particularly for drugs with a longer time to onset (e.g., lorazepam).
   6. If a physician is not present, the nurse should be given appropriate latitude to increase dosing to achieve specific goals, such as to reduce tachypnea to less than 25 breaths per minute.

F. *Orchestrating withdrawal of therapies.* There is great variation in how clinicians proceed with the withdrawal of life support. There are, however, a few common principles to guide clinicians.

   First, any medical treatment that is not essential to the comfort of the dying patient may be withheld or withdrawn. Artificial nutrition and hydration is a medical

treatment like any other but, unlike most, has strong cultural associations with nurturing and caring. It is important to be aware of the strong feelings that nutrition and hydration carry for many people, including caregivers. Although the medical evidence suggests that there is no additional benefit to continuing artificial nutrition and hydration, families may have cultural traditions of caring for the dying that make a decision to forego such therapy very troubling.

Once a decision has been reached to withdraw life support in a critically ill patient, one must neither prolong dying unnecessarily nor act to hasten it. The former is the more common mistake. A piecemeal withdrawal of therapies that stretches over hours to days is inappropriate (127). In the vast majority of cases, the patient cannot survive without the technology in question, and death is not only expected but imminent. When a decision is made to withdraw life support, then life support should be withdrawn—all of it. Removal of most therapies does not cause distress. These therapies, therefore, should be stopped rather than gradually reduced. The only therapy in which removal commonly results in exacerbation of symptoms is mechanical ventilation (see below).

One reason for the gradual withdrawal of therapies over days is to create distance between the removal of the medical intervention and the patient's death. Such space is neither legally nor ethically necessary (55,56). However, too close an approximation of death to the withdrawal of therapy is frequently uncomfortable for caregivers and may contribute to a sense of guilt among family members. More important, the time between withdrawal and death is frequently an important vigil for the family: Having made the decision to stop therapy may allow them to sit in the presence of the dying.

Withholding and withdrawal are supported by a broad ethical and legal consensus. Euthanasia is nearly as universally condemned. It is also illegal in Canada and the United States. Medications that hasten death but have no role in providing comfort, such as potassium chloride, should not be given. Similarly, if not quite so starkly, large bolus doses of sedatives and analgesics should not be given unless and until routine doses have proved ineffective in controlling symptoms. These medications should be titrated up to effect from below, not down from doses that may induce hypotension or apnea. NMB are frequently used in critical care to facilitate mechanical ventilation. Their therapeutic effect makes symptom assessment all but impossible. Their use at the end of life, when symptom control is paramount, is discouraged. There is some evidence that they are used, and sometimes started, in anticipation of withdrawal of life-sustaining therapy (54). Most intensivists recommend stopping any NMB when the decision is made to withdraw life support and in advance of withdrawing mechanical ventilation (128).

G. *Removal of mechanical ventilation.* Removal of assisted ventilation or an endotracheal tube commonly causes visible signs of distress even in patients comatose from their illness. The goal of ventilator withdrawal is to remove support efficiently over 15 to 30 minutes while maintaining patient comfort. In general, all other lifesustaining therapies should be removed first (Table 79-8). A common concern is whether to leave the endotracheal tube in place (sometimes referred to as *terminal weaning*) or remove it (extubation) (127,129). In patients who can support their own ventilation, even briefly, extubation may improve patient comfort. It allows closer contact between the patient and loved ones, and may improve communication. It is recommended to leave the endotracheal tube in place in patients on high levels of ventilatory support, who may die immediately if extubated, and in those with difficulty clearing secretions or protecting their airway, who may struggle and gasp when extubated (121).

TABLE 79-8. WITHDRAWAL OF MECHANICAL VENTILATION

H. *After-death care*. A physician should acknowledge and confirm to the family when the patient has died. Every intensivist should understand the nature and management of grief and bereavement (130). Recognize that families may second-guess themselves and may need reassurance that their decision was appropriate and correct.

A multidisciplinary team should debrief after every death, to review the technical details of the outcome, to examine the process of decision-making among the team members and to allow the team itself to express grief over the death of a patient. This is particularly important in cases where the decision was particularly difficult (young person, tragic circumstances, a person connected to the medical community) or where there was disagreement over the decision.

SUMMARY: IMPLEMENTING PALLIATIVE CARE IN THE INTENSIVE CARE UNIT

Institute mandatory family meetings with the attending physician within 24 hours of admission. Goals of this meeting are

A. To convey information about the patient, specifically, to review the reason for admission, the treatment plan, and the expected prognosis, along with anticipated decision points;
B. To orient the family to the ICU. Clinicians may avail themselves of novel technologies, including written brochures, videotapes, and interactive CDs, to help families understand the people and routines of the ICU (79);
C. To convey a strategy about future communications. The clinicians should identify the responsible physician(s) and nurse(s) and establish a plan for ongoing communications. This plan should offer daily communication between the family and a designated physician, preferably the attending or a critical care fellow; and
D. To reassure the family of their access to information about sudden changes in the patient's condition. The family should be able to call into the hospital at any time to obtain information about the patient. The hospital must be able to contact the family in the event of a change in status. This may involve loaning a beeper/ pager to the family.

Highlight the value of good communications skills. Specific areas of need include communicating bad news, group dynamics, how to conduct a family meeting, and how to invite patients into the process of decision making without making them responsible for decisions that may end with the death of the patient (131). Explicit attention needs to be paid to the dynamics of conflict and the importance of negotiating rather than imposing resolution to disagreements.

ICU staff should recognize that the same structural issues that affect communications with families—uncertainty, rapid changes in status, intense personal relationships, exposure to many patient deaths—also affect communication among physicians and between physicians and nurses. A hierarchical model that devalues the input of some members of the multidisciplinary team leads to dissension (3,132). Such dissension may adversely affect patient care (27).

Emphasize the importance of symptom management.One mechanism to accomplish this is to institute regular use of pain and sedation scales. Quantitative attention to symptoms will be especially needed if practice evolves toward reduced sedation to avoid prolonging ICU length of stay. As part of the emphasis on evidence-based symptom management, physician and nursing staff will need periodic reviews of pharmacology of opioids and sedatives and how their properties are altered in critical illness.

Formalize recognition of the importance of quality of dying and bereavement support through a systematic review of every ICU death. A senior physician and a nurse should institute a quality improvement project based on the review of the first 20 deaths. Bereavement training is essential for ICU staff to help them to recognize and to assist patients/families, as well as attend to the grief reactions that affect professionals who work with many dying patients (133).

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MEASUREMENT OF QUALITY OF LIFE OUTCOMES

ROLAND T. SKEEL

IMPORTANCE OF QUALITY OF LIFE OUTCOMES

Patients regularly ask physicians and nurses for quality of life information about their cancer and its treatment: “How much pain will I have? How much nausea and vomiting will the chemotherapy cause? How long will it last? Will I have enough energy to work? Is it safe for me to have sex? Will all my hair fall out? Will it come back? How much time will I have to spend in the hospital? How much is this all going to cost? When is my appetite going to come back? Why am I feeling so depressed? Will I ever stop being so nervous?” And they often ask the ultimate question that requires the physician to integrate knowledge of the anticancer treatment, the supportive care efforts, and the quality of life effect of the disease and the treatment: “Will I be better off because of this treatment?” Too often the answers given are limited to anecdotal, incomplete, or misinformed replies, because quality of life evaluations in cancer clinical trials and in palliative care have been uncommon, limited in scope, or difficult for the clinician to interpret (1).

The goal of supportive care in oncology—as is the goal of palliative care in any medical specialty—is to make patients function and feel better than they would have without that supportive care. This goal is explicitly different from that of curative or life-extending therapy, in which there is regularly a moderate to high tolerance for side effects and temporary functional impairments (2). Even with curative or life-extending therapies, supportive care measures are necessary, and the success of the palliative aspects of care may determine whether the patient is willing to tolerate repeated courses of the treatment, as is usually necessary with chemotherapy. Whether the care is given in conjunction with other cancer treatments or is used exclusively to palliate the effects of the cancer, the criteria for success are that the patient feels and functions better. When patients are less pleased with how they are feeling or functioning—that is, when they believe their quality of life is not better—then the supportive care has not been successful. The patients' personal, subjective perception of how they are feeling and how they are functioning thus becomes a critical outcome measure of this aspect of cancer care. As stated by Roy, “Quality of life studies and measurements are a systematic way of paying attention to the details in which effective compassion will be found or found wanting”(3).

HEALTH-RELATED QUALITY OF LIFE

Subjectivity of Assessments and Multidimensionality of Dimensions

Quality of life measurement is neither a concept nor a procedure with which nurses and physicians caring for patients with cancer are really comfortable, because it seems so difficult to define the meaning of the phrase “quality of life.” This is not to say that there is disagreement over the importance of quality of life. In two separate surveys of physicians in the Eastern Cooperative Oncology Group (ECOG), 63–89% of ECOG physicians said that they felt more satisfied when they could improve the quality of their patients' lives rather than simply prolong survival (1,4). Thus, even clinicians who have been self-selected to perform clinical research to find more effective cancer therapies value the notion of quality of life, despite lack of agreement on a precise meaning of the concept or the ability to measure it directly.

“Quality of life” is a phrase and a concept that also has crept into common parlance. When used in everyday language, it is assumed to cover many aspects of life, including the availability of food and shelter, climate, occupation, and other aspects of economic well-being, as well as social, psychological, and physical health. An article about the Federal Emergency Management Agency's report on “Nuclear Attack Planning Base—1990” discussed optimistic and pessimistic predictions about “the quality of life after World War III” (5). When measured in general populations by social scientists, “quality of life” usually refers to these broader terms. Domains that national surveys have identified as important to quality of life include the following:

- Physical and material well-being (which includes health and personal safety)
- Relations with other people
- Social, community, and civic activities
- Personal development and fulfillment
- Recreation (6)

Specific instruments used to measure quality of life determine the precise meaning for an individual study more definitively, and it is important to recognize that a single definition does not apply equally to all quality of life measurements. It is of interest that health and personal safety were ranked as important or very important by 95–98% of a sample of 3000 30- to 70-year-old subjects from the general U.S. population, higher than any other of the 15 different components that were ranked for importance to their quality of life. Only fifteen to 20% reported that this component was moderately, only slightly, or not at all well-met in their lives (6).

When limited to the narrower realm of illness and health, “quality of life” takes on more specific meanings, although it remains multidimensional and is clearly affected by factors that may be included in the more broadly designated “quality of life.” For the remainder of this chapter we use the term *health-related quality of life* (HQL) to designate a more focused concept related to the impact of a medical condition or its treatment on a person's expected physical, psychological, and social well-being. Calman has posited that quality of life evaluations measure the difference between the “hopes and expectations of the individual and that individual's present experiences” (7). This postulate carries the implication that the perceived quality of life could be improved either by reducing expectations or by improving the actual symptoms, functional status, and psychological well-being that the patient compares with his or her expectations. The reduction of expectations in HQL may be closely related to adaptation to changing health, as discussed by Schwartz and Sprangers (8).

Implicit in these definitions of HQL is that the designation of the extent of variation from that expected by the patient must be determined by the individual to have the greatest validity. Perceptions are, by their very nature, subjective. Therefore, reliance on family members or health professionals may produce misleading information on what the patient's quality of life is (9,10,11 and 12). In contrast to this general caveat, when treatment-related symptoms are focused on, others have found that, at least with some instruments, there are minor differences in HQL (13).

Although it is possible—and logical—to draw some conclusions about relative HQL impairment from certain symptoms or objective functional impairments, what appears logical may not in fact be the case. Two studies in patients with advanced cancer demonstrate this (14,15). In these studies, despite increased side effects from a more aggressive regimen (colon cancer) or a more prolonged regimen of chemotherapy versus shorter radiotherapy (lung cancer), patients did not report greater impairment of quality of life. It has been suggested that the overall improvement in quality of life in such active therapy may be related to “optimism and support provided by close medical supervision”(16).

It becomes even more hazardous to try to extrapolate the effect on psychological or social components of perceptions of HQL from objectively measured impairments. The subjectivity of HQL comes about in part because a person's designation of perceived HQL is psychologically derived from both his or her current (momentary) self-observed quality and the current quality that the person expects. The current quality expected is not static, but varies with many factors, including psychological adjustment to disease (e.g., the long-term paraplegic who is quite satisfied with his or her quality of life), culture, and personality. The momentary self-observed quality

of life is itself derived from a complex integration of factors that constitute the multidimensionality that is commonly assessed in quality of life measures (17,18 and 19):

1. Physical symptoms of the disease or its treatment or concurrent illness
2. Functional capacity (ability and energy) for daily routine, social interactions, intellectual activity, emotional reactions and adjustments, economic independence
3. Self-perceptions of wellness or its absence

The physical symptoms of disease and side effects of treatment that are common include fatigue, pain, nausea and vomiting, hair loss, and anorexia. Other symptoms of disease and treatment are quite specific to a disease or treatment and include problems such as incontinence of stool or urine, dyspnea from congestive heart failure or pulmonary toxicity, and peripheral neuropathies. Although these are discrete elements that contribute to global HQL, they also have an impact on functional capacity. The latter is usually separated into three distinct domains: psychological functioning, social functioning, and physical functioning. Psychological functioning includes anxiety, depression, adjustment to the disease and its treatment, and satisfaction with care. Physical functioning includes mobility, ability for self-care, and ability to carry on daily routine (e.g., child care or work activities). Social functioning includes family interactions, relationships with friends, and ability to function on the job beyond the physical level. Additional considerations in HQL may relate to spiritual concerns, sexual functioning, and body image (20). Variability among respondents may also occur because of the assessment environment, and the manner and form of evaluation (21). Thus, subjectivity and multidimensionality are two critical factors in understanding and measuring HQL and in interpreting data from HQL assessments.

QUALITY OF LIFE OUTCOMES IMPORTANT TO CANCER PATIENTS

Somatic and physiological symptoms and complaints are generally the most immediate concerns of patients with cancer. Dame Cicely Saunders, the founding director of St. Christopher's Hospice, London, England, stated at a lecture at Yale in the early 1970s that when a patient is in pain or lying in a bed of feces, it is difficult to converse with family and friends and to reminisce about the good times. The simple physical problems must be addressed first. “Successful symptomatic treatment should enable a patient to be so relieved of physical distress that he is freed to concentrate on other matters” (22).

Physicians and nurses are usually attuned to the physical, symptomatic distress expressed by patients. How likely it is that the range of HQL effects of this distress will be addressed depends on a willingness to take time with the patient and to ask appropriate questions that are relevant to the patient's disease. Even with the emphasis of the importance of HQL in cancer care over the past 10 years, patients express more concern and spend more time trying to discuss palliative care questions than physicians, who tend to focus on medical and technical issues (23). Asking the appropriate questions requires a knowledge of how specific factors about the disease and its treatment are likely to affect the patient's HQL. It also takes a recognition that these issues are paramount to many patients, and willingness to spend the extra time is needed to listen and offer thoughtful supportive responses.

Influence of Cancer Characteristics on Health-Related Quality of Life

The types of symptoms and physical distress experienced by patients are greatly influenced not only by the type of cancer but also by the stage of the disease, the specific organs and tissues involved, and the current or most recent treatment. For example, in early breast cancer, paresthesia on the chest wall consequent to surgery, nausea and vomiting, hair loss, or weight gain from chemotherapy may be important quality of life concerns. In advanced breast cancer, bone pain, loss of appetite and cachexia, or shortness of breath may be predominant physical quality of life concerns. For any patient who has completed active therapy, primary physical concerns may be persistent lack of energy with its resultant functional deficits, loss of organ function (e.g., of speech or swallowing), or the potential for second malignancies. As with other dimensions of HQL, patients' expectations about how they should feel play an important role in the degree to which their physical problems affect their reported HQL.

The influence of the cancer, its stage, and its treatment on the social and psychological domains of HQL are not as evident as with the physical domains. In contrast to somatic and physiological symptoms and complaints, social and emotional issues get inadequate attention from physicians and are underemphasized in many HQL measures (23,24). Physicians often feel that emotional support is better relegated to other health professionals, whereas many patients prefer to get their support from their primary oncology physician (16). The emotional benefit of psychological interventions for patients with cancer in reducing emotional distress, enhancing coping, and improving “adjustment” have been well demonstrated (25). There is even some suggestion that there is a physical, lifeprolonging benefit as well (26), although this is far from being established (27).

Influence of Age and Other Factors on Health-Related Quality of Life

Any discussion of HQL measurement must also recognize that HQL is influenced by considerations other than the disease in question and its therapy. Because the measured quality of life is dependent on expectations as well as the patient's current situation, anything that can affect expectations can have an influence on the measured quality. Younger people have different expectations regarding life expectancy than do older persons; they may also have different expectations about functional ability, pain, or other symptoms that could affect their perceived HQL. Age has been found to affect decision making by patients with cancer when they are presented with scenarios in which survival can be traded for quality of life: Younger patients are more likely to accept a treatment with more severe side effects to gain an increment in survival than are older patients, who have a greater interest in maintaining their current quality of life (28). In addition, patients with higher scores on the social well-being subscale of the Functional Assessment of Cancer Therapy (FACT) assessment, as well as those with children living at home, were more willing to have aggressive cancer treatment (29). Debilities from the disease or comorbid conditions may be greater in older patients and result in a worse baseline quality of life.

It has been found that older patients with cancer had lower HQL scores when uncorrected data were used. However, once complicating comorbidities or performance status were controlled for, the older patients had a quality of life similar to that of younger patients, according to various physical and psychosocial scales (30). Because the results obviously reflect how the analysis is designed and what measure is used, it is not possible to generalize from these data that age was not a factor in HQL measurement or perception. In fact, the opposite might be true, because only after “correction” for performance status or comorbidities or functional status were the HQL scores similar. Age is clearly a potentially important patient variable to be taken into consideration and controlled for when possible.

Similar arguments can be made for socioeconomic status, which has a significant effect on overall health (31). Because the cultural context in which the HQL is being evaluated is important, a determination of cross-cultural validity of HQL assessments is essential (32). Finally, personality factors, such as ability to adjust to and cope with stressful situations, can also have an impact on the patient's perceived quality of life, as they impinge on the patient's expectations (8).

Evolution of Health-Related Quality of Life Measurements from Curiosity to Commonplace

When Spitzer reviewed the state of the science of quality of life, he found only four papers in the medical literature (by physicians and surgeons) with “quality of life” in their titles between 1966 and 1970 (33). In the next 5 years there were 34, and since then the rise has been seemingly exponential: In 1993 alone, 165 articles met the specific criteria of focusing on HQL and were believed to be significant contributions to the HQL literature (34). In 2000, more than 5100 titles indexed in Medline's PubMed (National Library of Medicine, Bethesda, Maryland) contained the phrase “quality of life.” The growth of the area is further attested to by the fact that there is now a dedicated journal, *Quality of Life Research*, to deal with this topic.

Along with the growth in the research has been a concomitant growth in instruments to measure quality of life. Even 10 years ago, a review of a quality of life bibliography and measurement instruments found that over 170 different HQL instruments were reported as being used (34).

Many HQL instruments are designed for use either in the general population, to assess health status, or in patients with disease states, but they are not directed specifically at any one health problem (35,36). Other measures are much more specific and are designed with a limited population in mind, such as patients with systemic lupus erythematosus, chronic lung disease, or cancer. Even within disease groups, there are specific measures that aim to address the particular problems posed by a unique group of patients. For example, within cardiovascular diseases, there is a questionnaire for patients with chronic heart failure. Whether the approach is broad and general, or narrow and specific, the aim is to gain information that enhances understanding of the disease process, the illness that people experience from their diseases, the consequences of the therapy for the diseases, and the predictive value of the information about groups or individuals with disease.

Just as there is often a gap between patients' expectations about their HQL and current reality, there is also a gap between the health profession's affirmation of the importance of quality of life in medical care and how the outcomes from measurements of HQL using standardized instruments are used to inform patients, shape clinical decisions, and establish health policy. As a consequence, physicians continue to use unsystematic approaches to learn about their patients' perceived quality of life and to apply this knowledge to clinical decisions.

Although HQL evaluations in oncology, particularly in clinical trials (37,38 and 39), became prevalent somewhat later than HQL evaluations in cardiovascular (40) or chronic lung disease (41), there has been a flurry of activity in the past 10–15 years that has resulted in HQL evaluations being companion studies or an integral component of many clinical trials in oncology (38,39,42,43).

The most prevailing use of HQL assessment in oncology is as an end point in clinical trials (20,21,32,37,38,42,43,44,45,46,47,48,49 and 50). Gotay and colleagues (44)

suggested that for HQL to serve as a study end point, two conditions must be met:

1. The predicted survival differences between treatment arms are expected to be small.
2. Moderate to large differences are expected on at least one quality of life dimension.

This set of conditions describes one important situation in which HQL should be an end point, but if applied strictly it may be unduly restrictive to investigators who may have valid reasons to study HQL effects in other situations. For example, significant differences in HQL could be important to some patients despite substantial (or at least statistically significant) differences in survival. A determination of what is a “small” difference in survival, after all, requires a value judgment: a judgment of the relative importance of survival and quality of life to the patient. Importantly, a significant change in survival or HQL as seen through the eyes of the statistician may not be viewed as clinically important by the patient or physician. As pointed out by Edlund and Tancredi (51), to understand quality of life measures we need to know “who is talking about quality of life? What sort of quality is being specified? Defined by whom, for whom? Decided by whom? One must consider the different social and economic (or bureaucratic) groups who use the phrase, when they use it, how they use it, and finally, why they use it.” Predictability about preferences is treacherous, and contrary to some expectations, patients with cancer may forego a better quality of life and choose a more radical treatment with minimal chance of benefit than those without cancer, including medical professionals (52).

Use of Health-Related Quality of Life to Inform and to Develop Health Care Policy

Once HQL data have been derived from clinical trials that are deemed valid and generalizable, several uses can be made of the information. One obvious and direct use is to enable health care professionals to better inform patients about the risks and benefits of a proposed treatment, particularly if the alternatives being considered are the same as those that were compared in a clinical trial. Because HQL data may be a useful prognostic variable (53,54,55 and 56), they can be of further benefit to clinicians and patients in helping them to make informed treatment decisions. HQL data may also be used to evaluate the impact of socio-economic or ethnic factors on quality of life (57). HQL data have also been used—and some think misused—to influence an increasingly involved and interested public through mass public advertising for products as diverse as allergy medicine, hematopoietic growth factors, and therapy for impotence. The jury is still out regarding whether the net effect of this will be improvement in health or public HQL.

Thus far, most HQL evaluations have been attempts to learn about the impact of cancer and its treatments on groups of patients. This has led to a focus on disease rather than individual patient outcome. As familiarity with HQL assessments increases and their value and limitations become clearer, it is anticipated that they will become an aid in patient management, because (a) they have prognostic value, (b) they can be used as independent outcome measures that help determine the benefit or harm of current antineoplastic or supportive therapy, and (c) they can be used as clinical tools to direct earlier initiation of psychological, social, or physical support or rehabilitative measures.

Quality of life data can also be used to determine health policy (58). The information might be used to select alternatives for additional clinical trials or to make decisions about approval of new drugs for marketing. The U.S. Food and Drug Administration has declared that “a favorable effect [of an anticancer drug] on survival or quality of life is generally required for approval” (59). Assessments of HQL have the potential to enhance decision-making about the use of health care resources, but because of the pervasive issues of value that are associated with various HQL outcomes (or lack thereof), the information thus gained is open to misuse. As pointed out by Ganz, it will “be imperative that the QL data incorporated into policy decisions be of high quality and that both patient advocates and clinicians play an important role in their interpretation” (20). “The diffusion of process and outcome measures into practice; the practicality, reliability, and validity of these measures; and the impact that these indicators have on practice patterns and the health of populations will be key to evaluating the success of such quality-of-care paradigms” (60).

MEASUREMENT OF HEALTH-RELATED QUALITY OF LIFE

Clinical Assessment

Physicians have placed a premium on the quality of life of their patients throughout the history of medicine. Hippocrates wrote: “I will define what I conceive medicine to be. In general terms, it is to do away with the sufferings of the sick, to lessen the violence of their diseases, and to refuse to treat those who are overmastered by their disease, realizing that in such cases medicine is powerless” (61). In most clinical oncology offices, physicians regularly obtain HQL information from their patients when they ask “How are you?” or “How's it going?” This question is equivalent to the global HQL evaluation that asks, “How would you rate your quality of life today?” or “How satisfied are you at present with your life?” (62). The physician then follows up this question with further questions that probe the ways in which quality of life has been affected by the cancer and its treatment. This assessment is usually qualitative rather than quantitative, but it explores those domains that patients believe have an impact on their quality of life. For example, one patient may have low satisfaction with his or her current quality of life because of persistent nausea, another because of pain, and another because of a disinterest in talking with friends. These clinical assessments are essential in dealing with individual patient concerns, but they are of little value in collating information about the general and particular effects of cancer and its treatment on the “average” patient. For these purposes, standardized evaluation instruments are needed.

Standardized Instruments

To obtain useful information from groups of patients about HQL, standardized instruments are necessary (24,32,37,38,62,63,64,65 and 66). Questions that are asked of patients can fall into two major categories: They can be *open questions* to which the respondent may make any response, or *closed questions*, in which the respondent is supplied with a list of responses or a fixed scale on which to indicate a response. Open questions are less likely to restrict possible responses, but they are more difficult to categorize and analyze than responses to closed questions and may not cover all important areas because of the patient's reluctance, memory lapses or impairments, or lack of understanding of the scope of acceptable responses (66,67).

Psychometric and Utility Approaches to Health-Related Quality of Life Evaluation

Cella has emphasized that there have been two different approaches to measuring quality of life: *psychometric* and *utility* (68). With the *psychometric approach*, instruments are used to measure the impact of the disease, condition, or treatment on the physical, psychological, social, and functional domains of HQL and on overall perceived wellbeing. This approach does not quantify the weight or importance that patients place on these HQL domains or individual components when it comes to making decisions about alternative treatments, nor does it assess the impact of each component on their overall quality of life. For example, nausea and vomiting or anxiety may be rated by the patient as severe, but that alone does not tell the investigator how important it is to the patient's feeling of (or absence of) well-being, and further, how that will affect choices of therapeutic alternatives.

The *utility approach* is concerned with decision making and a comparison of two different conditions or treatment approaches in which an assessment is made by the investigator or the patient of the cost-benefit ratio of therapy. When utility measurements are made, there is always an explicit or implied evaluation of relative importance. The psychometric approach assesses intensity of symptoms, ability to function, and the psychological state of the patient; the utility approach tries to assess the importance of these factors, relative to each other or other factors, and the impact that they have on practical decisions (69). Utility assessments may involve

1. Offering theoretical choices between the patient's current state of health and various probabilities of cure or death
2. Asking the patient how much time he or she would be willing to give up to live the rest of life in perfect health
3. Having the patient subjectively assign the effect of specific HQL impairments on overall quality of life (24)

One current area of development in standardized instruments is to blend the psychometric data with utility estimates in the anticipation that the results will facilitate more informed decision making by individual patients, physicians, and policy makers. This kind of extension of HQL data permits formal assessments of various derived costutility parameters. In one type of analysis, total survival is adjusted for quality of that survival to obtain a measure called *quality of life years* (QALY). One can then compare treatments and calculate the cost for the gain in QALYs. This information can be used to address broad societal questions that involve comparisons between the value of incremental years lived and the costs for interventions under consideration relative to other health care or societal costs. One criterion states that treatments are reasonably cost-effective up to $50,000 per QALY gained (58). When patients themselves are asked about preferences for therapy, there is a reluctance to trade off survival for quality of life (70). This is consistent with the results of Slevin (52), who found that patients were more likely than doctors and nurses to accept radical treatment for minimal benefit.

The majority of HQL instruments in use today are based primarily on the psychometric approach. Examples of 17 generic, cancer-specific, and cancer site–specific instruments are reviewed elsewhere (71). Their application to cancer clinical trials has been reviewed by Moinpour et al. (38) and Maguire and Selby (72).

Development and Testing of Instruments

The design of a valid, reliable, and useful instrument is not as simple or straightforward as picking some questions that are thought to be important to quality of life,

applying a scale, and administering the instrument to patients. In the best-tested instruments there is a systematic process of item generation, item review and reduction, scale construction and piloting, and initial evaluation. Included in the initial evaluation are item analysis, factor analysis, creation of subscales (if there are to be any), and validity testing. Additional evaluation includes test-retest reliability and measurement of sensitivity to change. Validity testing tries to answer this question: Does the instrument measure what it is intended to measure? Measures of validity include

1. Content validity—does the measure cover all of the issues of interest and appear to be applicable for the stated purpose?
2. Construct validity—does the measure correlate with other similar measures completed at the same time, and do the results diverge from dissimilar measures completed at the same time?
3. Clinical validity or interpretability—are there correlations with other measures of health status, is there a responsiveness to a change in health status over time, and do the results have clinical relevance?

Once the instrument has undergone development and initial assessment, repeated evaluations over time in different populations are required to determine its specificity for unique populations and generalizability to broader categories of patients or healthy people.

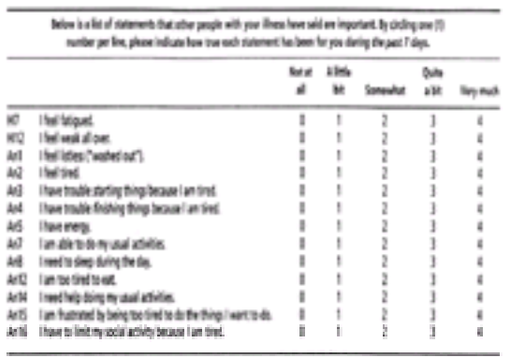
Generic versus Specialized Instruments

In the search for a gold standard, it was once believed that the choice was between either a broad generic instrument that gave information about general health status and HQL but was not specific enough to detail information relevant to a disease or treatment, or a specific instrument designed for each disease or stage or treatment. Aaronson (73) suggested an alternative modular approach whereby one could design an instrument with a number of general questions that would apply to many situations (e.g., to all patients with cancer) and append to this a module of diseasespecific or even trial-specific questions of disease symptoms and treatment side effects. This approach has been carried out by Cella and colleagues (24) and Aaronson and colleagues (32). A related approach uses an established general health measure, such as the Short-Form Health Survey: Medical Outcomes Study (35) and combines this with a global measure of quality of life and specific measures for anticipated disease and treatment-specific HQL outcomes, such as unique symptoms.

Examples of Health-Related Quality of Life Instruments in Cancer

The FACT measurement system is an example of a psychometric instrument (24). The FACT measurement is a 34- to 50-item compilation of a generic core of 34 items and specific subscales that can be appended for specific diseases. These subscales reflect symptoms and other problems that may be associated with disease sites (e.g., lung, breast, bladder, cervix, colon/rectum, head and neck, ovary, or prostate) or with human immunodeficiency virus infection. Table 80-1 provides an example of one of these instruments, the FACT-L (Lung) (74). The first 27 items correspond to the FACT-G (General), which can be given to any patient with cancer. The second set of ten items are specific for patients with lung cancer. The FACT is broken into five components from which subscales can be derived: (a) physical well-being, (b) social/family well-being, (c) emotional well-being, (d) functional well-being, and (e) additional concerns (disease-specific, treatment-specific, or both). A special concern has been the evaluation of fatigue, which is a common symptom associated with many cancers and cancer therapies. Fatigue may be amenable to therapy, such as weekly injections of erythropoietin for those with anemia-related fatigue. Table 80-2 provides an example of a specialized stand-alone instrument (The Functional Assessment of Chronic Illness Therapy—Fatigue) to evaluate fatigue, which has been validated in anemic patients with cancer (75).

TABLE 80-1. THE FUNCTIONAL ASSESSMENT OF CANCER THERAPY-LUNG (FACT-L) HEALTH-RELATED QUALITY OF LIFE INSTRUMENT



Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.						
		Not at all	A little bit	Somewhat	Quite a bit	Very much
HI7	I feel fatigued.	0	1	2	3	4
HI12	I feel weak all over.	0	1	2	3	4
An1	I feel listless ("washed out").	0	1	2	3	4
An2	I feel tired.	0	1	2	3	4
An3	I have trouble starting things because I am tired.	0	1	2	3	4
An4	I have trouble finishing things because I am tired.	0	1	2	3	4
An5	I have energy.	0	1	2	3	4
An7	I am able to do my usual activities.	0	1	2	3	4
An8	I need to sleep during the day.	0	1	2	3	4
An12	I am too tired to eat.	0	1	2	3	4
An14	I need help doing my usual activities.	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do.	0	1	2	3	4
An16	I have to limit my social activity because I am tired.	0	1	2	3	4

TABLE 80-2. THE FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY-FATIGUE (FACIT-FATIGUE) HEALTH-RELATED QUALITY OF LIFE INSTRUMENT

Questionnaires such as FACT are usually completed by the patients themselves, with instructions by a research assistant or nurse, but without assistance in completing the questions. The importance of patient-assessed HQL has been confirmed in cardiovascular disease (10) and cancer (11,76). After completion of the questionnaire, the nurse or research assistant reviews the responses to help ensure that all questions are completed (if possible) so as to minimize the number of unanswered questions. For patients who have difficulty in completing the questionnaire by themselves, it is preferable to have a nurse or research assistant help with the questions, because family members are more likely to insert their own biases about patients' responses than a person who has been trained to be neutral. Results are then analyzed by use of a manual provided by the developer of the instrument.

Although instruments such as the FACT are not widely used in the clinic to inform health care professionals about their patients' ongoing quality of life concerns or to make individual decisions about patients, adaptation of these selfadministered instruments to this purpose should be feasible, particularly as the health care professionals become more familiar with the instrument and with the interpretation of individual responses.

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (32,77) is a similar core questionnaire developed by the EORTC. It has an additional virtue of having consistent reliability and validity across three language-cultural groups: patients from English-speaking countries, those from northern Europe, and those from southern Europe. It does not ask patients to render a judgment regarding how much each of the domains (e.g., social well-being) affects their quality of life, although it does ask global questions about how patients rate their overall physical condition during the past week and how they rate their overall quality of life during the past week. The selection of the question time frame is influenced by the disease and treatment under study: If one is looking at a relatively short duration of side effects, then there must be a clearly defined time of interest in the questions. This also relates to the timing of administration of the instrument relative to the treatment. As pointed out by Aaronson, even in the case of long-term effects, the use of a relatively short time frame, such as a week, minimizes problems associated with memory loss or a tendency over time to minimize or exaggerate symptoms or functional impairment (73).

A different type of instrument used in patients with cancer is the Cancer Rehabilitation Evaluation System, developed by Schag, Ganz, and others (64,78). This is a comprehensive list of 139 problems encountered by patients with cancer. Patients rate each problem on a 5-point scale. The first 88 items apply to all patients. The remaining questions apply to subgroups of patients. For instance, if a person does not have children, that section is skipped; if the person has not been employed, that section is skipped. A short form with 59 items has also been developed. It is intended particularly for use in research protocols in which repeated measures may be

needed and too much time needed for completing an instrument would be undesirable.

A third example of a quality of life instrument is a newly developed Hospice Quality of Life Index (79). This is a 25-item satisfaction questionnaire that has visual analog scales with adjectival anchors on each end of a 100-mm line on which the patient must make a single mark. Each item is then weighted by the patient relative to its importance for his or her quality of life. This instrument has been less rigorously tested and validated than the first two, but it may have broader validity for patients approaching the end of life who are receiving only supportive care. Even less studied are measures to evaluate quality of life in terminally ill patients (80). Additional validation is necessary to learn the most helpful ways to assess quantitatively HQL in populations of patients not on clinical trials, but for whom maximizing functional and sense of well-being is of paramount importance.

QUALITY OF LIFE OUTCOMES IN PATIENTS WITH CANCER

Quality of life outcomes in patients with cancer that have been assessed by well-validated instruments have become much more common in the past several years, although their interpretation and usefulness to the oncology community has not yet been fully realized (81,82). The largest number studies have been in breast cancer, with fewer studies in other types of cancer, and fewer yet in the supportive care or palliative care settings. Some have addressed palliative care offered by cancer treatment. Because HQL evaluations have mostly been developed for patients with specific cancers, some examples of what has been done and the types of results achieved are discussed in this section, followed by a description of the development of HQL in assessing palliative care and the potential for future directions both in research and in clinical care.

Health-Related Quality of Life in Breast, Lung, and Other Cancers

Breast Cancer

One early study of HQL was an evaluation of patients receiving treatment for advanced breast cancer using a linear analogue self-assessment (LASA) by Priestman and Baum (83). In one group of women with breast cancer, they evaluated HQL with this technique before and after 3 months of endocrine therapy. In another group, they compared subjective toxicity with two different cytotoxic regimens. Although the analysis was not highly sophisticated, they reached the following conclusions:

1. Patient age does not greatly influence the degree of subjective disturbance.
2. A smaller fall in the LASA score during the second cycle of chemotherapy suggested that patients tend to adjust to their side effects with time.

The National Institutes of Health Consensus Development Conference Statement, “Adjuvant Chemotherapy for Breast Cancer,” stated that: “The goal of adjuvant therapy is to significantly prolong survival while maintaining an acceptable quality of life” (84). Many HQL studies that have addressed primarily “psychosocial” problems have been done in patients receiving adjuvant therapy for breast cancer. For example, Meyerowitz (85) studied 50 women receiving adjuvant chemotherapy and found that 88% reported a decrease in activities from the adjuvant chemotherapy, 54% reported an increased financial burden, and 41% said their treatment had an adverse effect on their family or sexual life. Seventy-four percent said they would definitely recommend the treatment to their friends. This disparity demonstrates that the psychometric analysis (how much of a problem they have experienced) without the utility analysis (the relative importance of the symptoms versus possible benefits from treatment) gives incomplete information. A 2-year follow-up of 35 of these patients 21 months after treatment ended found that there were significant improvements in quality of life in most areas, although there were continuing problems in the physical area (86). Anxiety levels were found by Cassileth et al. to be similar in patients randomized to adjuvant chemotherapy versus observation in women in two Eastern Cooperative Oncology Group studies (87). Although the sample was small, the data were sufficient to rule out major differences in anxiety levels among women randomized to each arm.

The effectiveness of supportive care, such as for nausea and vomiting, clearly can make a difference in HQL outcome. The investigators in one early study of adjuvant chemotherapy in breast cancer and its effects on quality of life believed that the side effects from multiple drug regimens were so severe that they decided to stop a study of doxorubicin, vincristine sulfate, fluorouracil, methotrexate, and chlorambucil. Major side effects were nausea and vomiting, alopecia, and feeling “off color.” Nearly 30% of the patients said the treatment was unbearable or that they would “never again” undertake it (88).

Kemeny and associates looked at psychosocial outcome in 52 (62%) of 83 patients randomized to mastectomy versus segmentectomy (89). They found that women with segmentectomies felt less anxious, less sad, and more in control of their lives. Even the fear of recurrence was less in the segmentectomy group. Offering a choice of surgery in early breast cancer has been shown to reduce anxiety in both patients and their husbands (90).

Coates and others (46) looked at the HQL effect of intermittent versus continuous treatment strategies for advanced breast cancer and concluded that continuous chemotherapy was better than intermittent chemotherapy. In other words, it does not help to take a break and wait for the disease to progress. The implication is that cancer (or the concern about doing nothing for the cancer) has a greater adverse effect on HQL than does chemotherapy. Coates and colleagues have also looked at whether quality of life scores predict outcome in breast cancer. They found that there was minimal prognostic significance in the adjuvant setting, but that with relapse, poor HQL scores were strong predictors of shorter survival. They suggested that the patient's perception of disease severity influences HQL scores (91).

A different approach that tried to put some relative value on health states regarding adjuvant therapy of breast cancer was pioneered by Gelber and associates, who coined the concept “time without symptoms or toxicity” and a modification of it, the “quality-adjusted time without symptoms or toxicity” (47,92,93). Their studies supported adjuvant therapy as providing more quality time to patients, even when the toxic periods were subtracted from the total survival.

The palliative benefit of pamidronate disodium as a supplement to antineoplastic therapy has been evaluated in women with breast cancer and osteolytic metastases (94). Skeletal complications were reduced and pain scores better in the group that received pamidronate disodium. Fatigue has been increasingly studied in breast cancer as well as other cancers and therapies. In one study of breast cancer survivors, fatigue was found to be severe and persistent in approximately one-third of the women studied (95). Determination of the mechanisms underlying fatigue in this and other populations will aid in both prevention and more successful treatment. Menopausal symptoms occur earlier in women younger than 50 years of age when they receive cytotoxic adjuvant therapy for breast cancer. A comprehensive menopausal assessment and intervention program has been shown to be feasible and acceptable to breast cancer survivors, resulting in a reduction of symptoms and sexual dysfunction, but no demonstration of improvement in the RAND Short Form Health Vitality Scale (96).

Lung Cancer

In lung cancer, Cella et al. found that the psychological distress was correlated with worsening performance status and that when the performance status was poor, the extent of disease was also a determinant of distress (97). An early study in lung cancer using the Functional Living Index— Cancer found that when patients did not complete the instrument, not enough information was obtained for rigorous analysis (98), but correlations were found, as might be expected, between HQL and performance status. Compliance problems are not trivial, but there appear to be methods that minimize their occurrence (99). Psychological response has been compared in patients with lung cancer receiving either intravenous methotrexate, doxorubicin, cyclophosphamide, and oral lomustine (repeated in 21 days) or intravenous cyclophosphamide, doxorubicin, vincristine sulfate, and oral lomustine (with the doxorubicin and vincristine sulfate repeated in 21 days) (50). This study showed a “strong trend” to more fatigue and depression in the second group, which was hypothesized to be due to the vincristine sulfate, despite no differences in clinical response. It demonstrated the value of HQL studies in lung cancer or other cancers, although the conclusions themselves have no importance for current lung cancer therapy. Other studies, as mentioned previously, have shown that assessment of HQL can be a predictor of survival in lung cancer. Assessment of HQL by the Functional Living Index—Cancer is superior to performance status for predicting survival in patients with lung cancer (53,54). Other studies have failed to show that HQL is predictive of survival in lung cancer after adjustment for other factors, such as pain (100).

Systematic evaluation of symptoms at presentation in patients with lung cancer has shown that the chest symptoms commonly inquired about are not the only issues of concern to patients. Tiredness, lack of appetite, worry, and anxiety, as well as cough and shortness of breath, are most common, and are equally present in patients with both small cell and non– small cell carcinomas of the lung (101). The authors suggest that all symptoms at the outset of disease must be taken into account when the benefit of palliative therapy is assessed.

Other Cancers

Other cancers have been studied less regularly, although each common cancer, modality of therapy, and age group has probably had some HQL or psychosocial evaluation (49,102,103,104,105,106 and 107). Prostate cancer probably deserves special mention, as its potential prevention, diagnosis, and treatment have catapulted to prominence in recent years. Patients receiving a luteinizing hormone-releasing hormone agonist and flutamide in remission were studied using the EORTC questionnaire C30 and the Medical Outcomes Study Short Form Health Survey SF-36 (108). They were found to have a HQL that was not distinguishable from a matched male population without prostate cancer, but significantly better than men who were in progression from androgen resistant disease.

Health-Related Quality of Life in Symptomatic Care

In contrast to the burgeoning development of HQL assessments in clinical trials of cancer therapy, there has been less systematic advancement in the design of specific instruments or the use of standardized instruments for patients receiving supportive, palliative, or posttreatment follow-up care (80,109,110,111 and 112). In their literature review of the psychologic and psychosocial implications of survivorship of cancer in adults, Welch-McCaffrey and associates (113) point to significant psychosocial concerns of patients who have had cancer and are no longer undergoing active treatment. They include fear of recurrence and death, relationships with the health care team, adjustment to physical compromise, alterations in customary social support, isolationism, psychosocial reorientation, and employment and insurance problems. For many patients who are no longer undergoing active therapy, psychological and social support are necessary for optimal rehabilitation. Survivors of various cancers have been studied in a systematic fashion by use of validated instruments (114). One conclusion has been that patients who survive cancer do not return to a state of normal health, which emphasizes the need for continuing supportive care after active cancer treatment has ended. The relative absence of good prospective studies, however, has meant that retrospective studies, case reports, and legal overviews have been the primary source of information about such effects (113).

Farncombe (115) has suggested that the model for palliative care has shifted in recent years from one in which there was a sharp break between active aggressive therapy and palliative therapy to one in which there is a gradual shift in the balance between the approaches. This means that the HQL evaluations of palliative care must not be relegated only to patients who will no longer be offered active antineoplastic therapy, but can, in fact, take place throughout the course of management of the cancer (110,111,116,117). The need for supportive care as a key ingredient of total cancer care is being recognized by many National Cancer Institute–designated cancer centers that have ongoing research programs in supportive care (118). The prevalence of symptoms has been shown to be highly associated with psychological distress and poorer quality of life (119). This association highlights the need for regular assessment of HQL in the evaluation of symptom management during all phases of cancer care.

Occasional chemotherapy studies have been done in which palliation was the primary end point of therapy. Moore and coworkers (120) treated hormone-resistant prostate cancer with mitoxantrone hydrochloride and prednisone and used HQL as the end point. Evaluation tools included a pain intensity score and a modification of the EORTC core questionnaire. By these criteria, 9 of 25 patients achieved a palliative response lasting 6 weeks or more, despite the fact that only one patient had a measurable objective partial response. A larger study has confirmed these results (121). The drug gemcitabine hydrochloride was approved as firstline chemotherapy for cancer of the pancreas, primarily on the basis of its greater efficacy in achieving “clinical benefit response” (a composite of measurements of pain) than the previous standard agent, fluorouracil (122).

HQL has been compared in patients with terminal cancer who were dying in palliative care units or in the hospital. Using a variety of psychological scales, Viney and associates (123) looked at uncertainty, anxiety, depression, anger, helplessness, competence, sociability, and good feelings through content analysis of interview material. They found that patients in specialized palliative care units showed less indirectly expressed anger and more positive feelings. They also reported more anxiety about death, but less anxiety about isolation. Several studies have tried to determine whether palliative care has a positive effect on patients' HQL, but aside from patient and family satisfaction, benefit has been difficult to demonstrate (124,125,126 and 127).

A special problem pertains to children who are at the end of life. Many of these children die in the hospital, often in an intensive care unit. Parents reported to Wolfe et al. that 89% of the children suffered “a lot” or “a great deal” in their last month of life, most commonly from pain, fatigue, or dyspnea (128).

HQL has been found to deteriorate in most patients during the last weeks of life (129,130), although a substantial group (20%) of patients cared for in hospices felt that they had a good quality of life even toward the end of life (131). This suggests that attention to patients' concerns could play a role in the maintenance of HQL as perceived by the patients and that factors other than physical function are contributors to HQL in terminal cancer. When patients with varying prognoses were compared by use of the EORTC QLQ-C30, the main effect of prognosis was on the general quality of life scale and the physical aspects of HQL, with little effect on social or psychological functioning (116).

Compliance can be a major problem when trying to study patients who are at the end of life. Jordhoy et al. found that compliance in completing HQL questionnaires was good up to one month before death, but fell significantly in the last weeks of life (132). Because of the weak physical state of most patients who are terminally ill, Cohen and Mount (110) have suggested that the ideal palliative care HQL instrument is one that can be administered verbally (orally) in 10–15 minutes. They believe that the measure should determine how satisfied the patients are with the various aspects of their lives that are evaluated, and that they should be asked how important that aspect is to them (utility weight).

Single-problem issues can be important and legitimate foci for HQL evaluations in palliative care. In such circumstances, the HQL instrument may be limited to various facets of the single problem, such as the response of anorexia to megestrol acetate, which was reported to improve appetite and increase weight and food intake (133). Pain relief has been a common single-problem focus in the HQL arena. Studies of palliative pamidronate disodium in the treatment of patients with bone metastasis from breast cancer exemplify this (94,134). As an alternative to the study of only one symptom, broader instruments may be used to determine the impact of one problem on overall HQL.

Issues of feeding, nutrition, and hydration are among those that will benefit from more systematic evaluation of HQL. Patients who have been monitored during terminal illness to determine the frequency of hunger and thirst reveal that hunger is infrequent and can be usually be palliated by small amounts of food (135). Thirst can be relieved by careful mouth care and sips of water—less than would be ordered to prevent hydration. It is concluded that attention to what the patient requests is probably of greatest benefit to most patients. If patients have stopped eating, the production of ketones may lead to suppression of hunger and mild euphoria. Administration of carbohydrates (as in 5% dextrose and water) could serve to reverse this and reawaken hunger (136). If artificial feeding is deemed appropriate, the enteral approach should be used, if possible. Padilla and Grant (137) reported that even in those who had lost the normal ability to eat, enteral tube feedings gave patients more perceived control, were less stressful, and produced fewer psychosocial problems than parenteral feeding. Finally, vigorous attempts at hydration in patients whose heart and kidneys are failing may inadvertently lead to fluid overload, pulmonary congestion, and a more uncomfortable death than if the natural processes are allowed to take place.

An additional area of palliative care that is as least as difficult to study is the use of drugs for symptom control during the last days of life (138,139). Issues that must be addressed not only include the quality of the living and dying by the patient and the predominance of the patient's own wishes for the relief of suffering, but also the perceptions of the family about the patient's suffering and their own suffering. Consideration must also be given to ethical, social, and religious issues surrounding suffering and its relief by allowing death to occur in the process of relieving the suffering or withdrawal of mechanical ventilation and other life-support measures (140,141,142 and 143).

Although there is an obvious limit to when and under what circumstances HQL testing can be done, it may be possible to ask alert patients in the terminal stages of disease— using standardized questionnaires—how much relief or discomfort they experience from those things we do to try to help. Indeed, it has been suggested that many palliative care patients welcome the opportunity to participate in clinical research, because they recognize that they will receive stateof-the-art care and also that they will continue to provide meaning for their lives by contributing to society as they and their families deal with their life-wrenching illness.

One such study has been done by the Methylprednisolone Preterminal Cancer Study Group, which studied the effect of an 8-week course of methylprednisolone, 125 mg daily, in a double-blind, placebo-controlled trial (144). Assessment of HQL was made by use of the Nurses' Observational Scale for Inpatient Evaluation, the LASA, and the Physicians' Global Evaluation. In all scales, treatment was more effective in improving HQL but was associated with a higher mortality rate in females. The reason for the latter result was not established.

One problem in the evaluation of HQL in patients receiving cancer treatment is a high attrition rate (98). This is a particular problem in patients receiving palliative chemotherapy who may die during therapy or become too ill to be able to or wish to continue reporting on their HQL (132,145). This does not mean that HQL evaluations should not be done, but that the limitations of the population must be considered when studies are designed.

The Staunton Harold Sue Ryder Hospice used a method of assessing HQL at the time of patients' admission to their program that deliberately avoided standardized instruments. This was based on their opinion that standardized measures in the later stages of terminal illness were inappropriate because of poor patient acceptance, the “danger” of missing an aspect of suffering that was of most immediate concern to the patient, and the unreliability of observers' assessments of these patients' needs (146). They found this technique helpful in identification of previously unrecognized or underrated problems, particularly those that were psychosocial. They found that the use of the Patient Evaluated Problem Score was also helpful in evaluating progress and that it was acceptable to patients, even those who were within a week of dying. The authors recognized that this type of questionnaire cannot easily be used as a research tool, nor is it appropriate for inter-patient comparison.

Another approach to the evaluation of palliation is the “audit.” Such an approach can determine the perspective of health care providers on symptom relief, objective response, and improved activity status. This approach can be used to assess the cost-effectiveness of palliative therapy (147). Although this use of predetermined criteria for effectiveness is valuable and could be one component of the determination of effectiveness of symptom management, it is necessarily incomplete without

the patients' perspective obtained from HQL evaluations (148).

CONCLUSION

As society becomes more concerned about the cost of hightechnology care, legitimate questions can be raised about how to integrate the patient's subjectively determined quality of life into the formulation of total medical benefits and costs incurred with palliative care. The costs of care will be most problematic if the care given is seen as “futile” or “marginal” (149). Without a doubt, HQL measurements will be factored into clinical practice guidelines and policies by professional societies, insurance carriers, states, and perhaps the federal government.

It has been proposed that HQL tools will be more widely used in the future, so that oncologists will become as familiar with them as they now are with performance status and will find them equally useful (20). If standardized HQL scores are found to be reliable and clinically meaningful end points for groups of patients in clinical trials, they may become integral to the process of making individual patient treatment recommendations and decisions. The degree to which this happens will depend on the results of current clinical trials and the ease with which these results and their meanings are translated to individual patient scenarios by clinicians. Such a development is contingent on the maturation of HQL evaluations in clinical trials now under way, dissemination of the findings, and a demonstration of their discriminatory value for prognosis and for understanding the benefits and burdens of cancer therapy in cancer. If this comes about, such HQL evaluations may be able to identify problems that can be addressed immediately by the physicians or other members of the health care team. As Till et al. point out, it is not just those who are directly involved in HQL research who have legitimate priorities, nor even the health care providers, but especially patients and their advocates (81).

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81

OUTCOMES ASSESSMENT IN PALLIATIVE CARE

JOAN M. TENO

Accountability has been called the “third revolution” in medical care (1). Health care providers are now often faced with new questions. For example, what are the outcomes of palliative care that justify its continued institutional support? Or, what is the evidence for the use of a certain medical intervention for a specific patient? Fundamental to answering these questions are defining quality of care for seriously ill patients and determining how care is measured.

Quality care at the end of life is different than during any other period of time. Dying persons, their families, and health care providers are often faced with decisions that involve tradeoffs between length of life and quality of life. Reasonable persons may differ in such decisions. Thus, preferences and values are important to shaping treatment decisions in ways unlike other time periods. Outcomes assessment for the dying must take this into consideration. In this chapter, a practical approach to examining outcomes, whether it is part of an audit prior to quality improvement efforts or for the ongoing assessment of institutional quality of care, will be discussed.

WHY EXAMINE OUTCOMES?

The first response of staff to auditing the quality of care is, “Why?” A typical response is that their work can't be measured. Yet, audits and ongoing quality monitoring through examining administrative data, reviewing medical records, and/or speaking with dying persons and families, leads to important opportunities to improve quality of care. Simply stated, “If you don't measure it, you won't improve it” (2).

The results of assessing the outcomes of palliative medicine can help create the needed attention to the issue of improving the quality of care. Such tension can create the awareness among health care providers of opportunities to improve and enhance their current practice. Examining the outcomes can be critical to detecting early problems with new medications or other unintended consequences from medical interventions. Examining outcomes can guide organizational efforts to improve the quality of care. For example, knowing that one in four persons now dies in a nursing home provides important information for the planning of new programs to meet the needs of the dying (3).

WHAT OUTCOMES TO MEASURE?

Reflecting on the thirtieth anniversary of St. Christopher's Hospice, Dame Cicely Saunders said, “We have never lost sight of the values that were so important to David: commitment to openness, openness to challenge, and the absolute priority of patients' own views on what they need” (4). Fundamental to palliative care is meeting the needs and expectations of patients and families. Quality in a 42-year-old with an acute myocardial infarction can be measured by whether interventions have been done that minimize infarct size such as the use of aspirin or percutaneous transluminal angioplasty. The vast majority of persons would want efforts to focus on restoring function under these circumstances. On the other hand, the circumstances of a 42-year-old dying of stage IV lung cancer are quite different. Technological interventions require weighting of their impact on both quality and quantity of life—decisions that require the input of an informed patient.

The importance of preferences is reflected in the Institute of Medicine definition of quality of care: the “degree to which health services for individuals and populations increased the likelihood of desired health outcomes and are consistent with professional knowledge” (5). This definition implies that conceptual models for quality care (as well as instruments measuring quality) must be based on both professional knowledge *and* informed patient preferences. To date, most conceptual models have been built either around expert opinion *or* qualitative data from patients, families, or health care providers.

Fortunately, both experts and consumers agree in many ways about what is important for end-of-life care—physical comfort, emotional support, and autonomy. However, they have significant areas of disagreement as well, e.g., unmet needs (Table 81-1). Family members want more information on what to expect and how they can help their dying loved ones. Patients and families emphasize the importance of closure at the end of life, including issues of personal relationships. Families often speak of frustration with a lack of coordination of medical care. It often isn't clear who is in charge; different health care providers provide conflicting information, and transitions can be fraught with confusion (6).

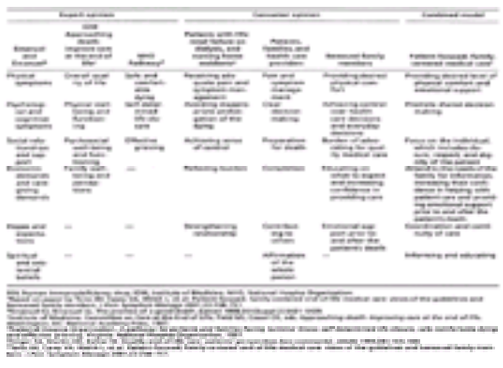


TABLE 81-1. COMPARISON OF DOMAINS OF EXPERTS, PATIENTS, FAMILY MEMBERS, HEALTH CARE PROVIDERS, AND PROPOSED COMBINED MODEL IN MEASURING QUALITY OF CARE AT END OF LIFE[a]

One conceptual model, Patient Focused, Family Centered Medical Care (Table 81-1) is based on a review of existing professional guidelines *and* results from focus groups conducted with family members (6). According to this model, institutions and care providers striving to achieve patient-focused, family-centered medical care for the seriously ill patient should

- Provide the desired level of physical comfort and emotional support
- Promote shared decision making, including advance care planning
- Focus on the individual patient by facilitating situations in which patients achieve their desired levels of control, staff members treat patients with respect and dignity, and patients are aided in achieving their desired levels of closure
- Attend to the needs of caregivers for information and skills in providing care for the patient, and provide emotional support to the family before and after the patient's death

Based on this model, a survey intended to be used as part of an initial quality audit of the quality of end-of-life care has been developed and validated.

HOW ARE OUTCOMES MEASURED?

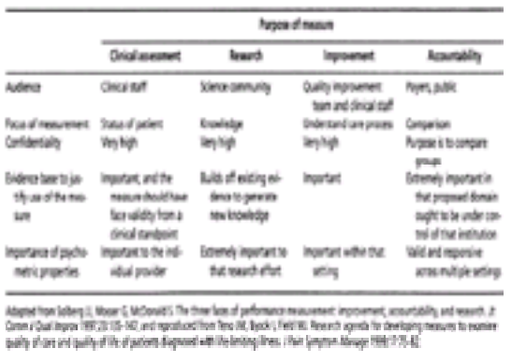
Outcomes assessment refers to measuring the “end results”—the impact or effect of medical care on the dying person and/or family. Measuring outcomes allows you

to judge the effectiveness of medical interventions, innovative programs, and new medications. In addition to examining outcomes, process measures provide important information for quality improvement and examination of the effect of new programs. A *process measure* examines what a service or intervention does for patients and their families. For example, a process measure focuses on whether there is regular assessment of pain noted in the medical record, while an *outcome measure* examines whether patients report that they received their desired amount of pain relief. Both are important and critical to measure. Ultimately, the quality of medical care is judged by changes in outcome indicators. Yet, an organization will not achieve those outcomes if it does not implement key processes of care that are known to benefit medical care.

Key to choosing an outcome or process measure is the intended use of the quality measures. Table 81-2 notes the four potential uses of measurement tools.

TABLE 81-2. PURPOSES OF QUALITY MEASURES

The areas of emphasis and desired characteristics vary for measurement tools intended for different purposes (Table 81-3). For example, the intended audience for quality improvement measures is the institutional and quality improvement team, whereas the intended audience for public accountability is the health care purchaser and consumer.



	Purpose of measure			
	Clinical assessment	Research	Improvement	Accountability
Audience	Clinical staff	Science community	Quality improvement team and clinical staff	Payers, public
Focus of measurement	Status of patient	Knowledge	Understand care process	Comparison
Confidentiality	Very high	Very high	Very high	Purpose is to compare groups
Evidence base to justify use of the measure	Important, and the measure should have face validity from a clinical standpoint	Builds off existing evidence to generate new knowledge	Important	Extremely important in that proposed domain ought to be under control of true institution
Importance of psychometric properties	Important to the individual provider	Extremely important to that research effort	Important within that setting	Valid and responsive across multiple settings

Adapted from Solberg LI, Mosser G, McDonald S. The three faces of performance measurement: improvement, accountability, and research. *J Comm J Qual Improv* 1997;23:135–147, and reproduced from Teno JM, Byock I, Field MJ, Research agenda for developing measures to examine quality of care and quality of life of patients diagnosed with life-limiting illness. *J Pain Symptom Manage* 1998;15:75–82.

TABLE 81-3. AREAS OF EMPHASIS BASED ON THE PURPOSE OF QUALITY MEASURE

Measurement tools used for public accountability need further evidence that justifies their use. For example, given the intended audiences and implications of the use of measurement tools for public accountability, more stringent psychometric properties must be used for these measures. In addition, there must be either normative or empirical research that substantiates a claim that the construct being measured for public accountability is under the control of that health care institution.

Typically, measurement tools can review the medical record, examine administrative data (such as death certificate or billing data), or conduct interviews with a patient or a proxy such as a family member. Each potential source of data has strengths and limitations that should be considered when selecting a measurement tool or strategy.

Medical records are legal documents that should reflect the medical care that patients receive. Yet, medical records reflect staff perceptions, and their contents are subject to reporting bias. For example, a nurse may document that a patient understands how to take his/her medications on hospital discharge; this documentation reflects the nurse's perception. Yet, patients and families often report that they did *not* understand that explanation when interviewed after hospital discharge (8). Furthermore, not all discussions are documented in the medical record. Discussions about resuscitation preferences are usually only documented when the patient or family consents to a “do not resuscitate” order. Thus, a physician and patient may have talked about resuscitation preferences and decided *not* to forgo cardiopulmonary resuscitation, but there is nothing documented in the medical record because cardiopulmonary resuscitation is the default in the majority of U.S. hospitals.

Administrative data, such as death certificate data, billing data, or the Minimum Data Set, is readily assessable information that can provide invaluable information. Examining death certificate data that is published on the internet (see www.cdc.gov) and available in public use files can provide hospice and palliative programs with information about their “market share,” i.e., what proportion of persons for whom they provide medical care in a certain geographic area. This information can highlight areas that are underserved and opportunities for program expansion. Users of administrative data need to be aware that it can be inaccurate because of coding problems, key punch errors, or economic incentives to upgrade a patient's condition to get more reimbursement.

The Minimum Data Set is used in U.S. nursing homes to systematically collect information on more than 300 items on a quarterly basis. This instrument can provide institution-specific and national estimates of outcomes, such as pain management (9). Yet, these data reflect staff perceptions of patients' levels of pain. Thus, ascertainment bias is an important concern in the use of these data.

Surveys, either self- or telephone-administered, provide information directly from the patient and family perspective about the quality of care. Typically, satisfaction measures which ask a person to rate the quality of care with response categories that vary from “poor” to “excellent” have not yielded discriminating information about the quality of care. The respondents' task with these rating questions includes several steps: First, determine whether that event occurred; second, formulate their expectations regarding that aspect of care; and third, choose a category from the response categories. Often, persons have lowered expectations regarding their medical care, which, at least in part, explains the finding of high satisfaction in the face of indicators of poor quality of care, e.g., severe pain (10,11).

Newer methods have begun using either “patient-centered reports” or “preference-based questions” (i.e., unmet needs) to capture the consumer perspective (Fig. 81-1) (12). These methodologies, unlike typical satisfaction questions that rely on ratings questions, provide information that guide improvement of the quality of care. For example, knowing that 85% of patients believe a health care provider is “very good” does not tell that provider in what ways and specific processes of care that he/she can improve. On the other hand, knowing that 20% of patients did not understand a provider's directions for taking pain medications does provide a tangible target for improving and enhancing the quality of care. Moreover, patient-centered reports and preference-based questions have strong face validity with health care providers. In the future, surveys need to rely on all three methodologies—ratings, patient-centered reports, and preference-based questions—to capture the consumer perspective on the quality of care at the end of life.

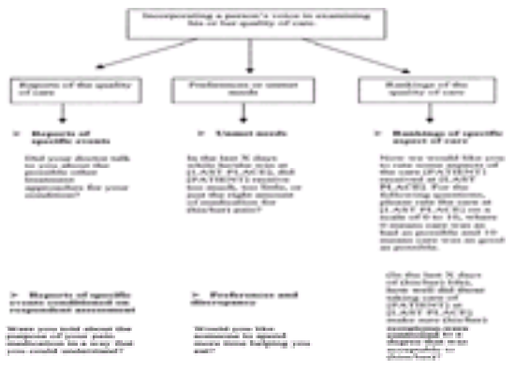


FIGURE 81-1. Proposed classification scheme for measuring a patient and family voice about the quality of medical care. [Adapted from Teno JM. Putting patient and family voice back into measuring quality of care for the dying. *Hosp J* 1999;14(3–4):167–176. Review, with permission.].

WHICH TOOL SHOULD BE USED?

Selecting a measurement tool should be guided by its intended use and the characteristics of the particular tool. The goals of measurement should be clear. As noted in Table 81-3, different psychometric properties (i.e., reliability, validity, and responsiveness of the tool) are needed for different intended uses. In addition, the intended audience is different for each of the four key purposes of measurement listed in Table 81-3. Measurement tools used for accountability, for example, have an intended audience of health insurers, the government, and other such institutions that pay for health care services. The focus of measurement is to compare health care institutions or plans. Given this purpose, it is very important that there is evidence that what is being measured is under the control of that health care institution and that the chosen instrument is reliable, valid, and responsive across the settings.

Reliability is necessary but not sufficient evidence of validity of an instrument or measurement tool. Reliability examines the degree to which the measurement tool is capable of reproducing the same results over time. Thus, a person should give the same response to a question if asked within a short period of time.

A measurement tool is valid if there is evidence that it measures what it purports to measure. In essence, one is asking whether the measurement tool is reporting the truth. Often, the intent of the measurement tool is to identify a perception or attitude of the respondent. In this case, there is not a “gold standard” by which to judge whether the measurement tool is accurately representing the construct that is being measured.

Content validity asks whether the measurement tool examines the correct concepts at face value. Were experts involved as advisors in the creation of the tool? Was the selection of concepts based on a theoretical model? *Construct validity* examines the degree to which the results from that measurement tool are associated with preestablished and known relationships. For example, a measure of overall satisfaction should be associated with consumer choice of health care plans.

Responsiveness examines the degree to which a measurement tool changes as a result of interventions or historical events. Often, responsiveness is not reported in the initial validation of a measurement tool. Rather, responsiveness is reported at a later date after the measurement tool has been utilized in intervention studies or research that tracks quality over time.

Over the past several decades, an increasing number of measurement tools have been developed for examining the quality of end-of-life care. A Web site maintained by the Center for Gerontology and Health Care Research at Brown University offers a structured literature review of existing instruments that focus on examining palliative care outcomes (see www.chcr.brown.edu/pcoc/toolkit.htm). This Web site is a good starting point for selecting measurement tools for quality improvement and research purposes. The site provides published instruments in ten domains and selects promising instruments for in-depth review, including psychometric properties and response burden.

For a seriously ill and dying population, the time burden on respondents and staff is an important consideration for selecting an instrument. Limiting the scope of domains covered and the number of individual cases for which data is collected can reduce time burden. For an interview respondent— especially a seriously ill patient—it is particularly important to limit the scope of domains that are covered in the interview. For the purpose of quality improvement, you do not need to collect a large number of cases. A small number of cases collected by a random sample can provide invaluable information to guide a quality improvement effort.

HOW IS THE SAMPLE SELECTED?

A fundamental, yet often perplexing, step is deciding who is to be included in the sample. This relates to the “denominator” for the outcome being measured. Simply stated, a rate is composed of a numerator and a denominator. Determining who is in the denominator can be difficult in palliative medicine. For example, three decades ago, most persons would have considered patients with childhood leukemia to be among those patients with a terminal illness. However, this no longer is the case due to the tremendous strides made in treating childhood cancers. Researchers and quality improvement teams, then, must make decisions about which patients to include in the overall group of interest (i.e., the denominator).

The difficulty of accurate prognostication is an additional issue. Physicians are often overly optimistic in their prognoses, resulting in uncertainty about patients' actual time before death. Even the best statistical models are inaccurate because they are applying historical information from a previous cohort of similar patients to predict the future. There is certain error in those estimates. Moreover, new treatments can invalidate even the best estimates by prediction models.

Although the timing of the interview is not as critical for certain domains, such as pain assessment, other domains are very sensitive to the time from death at which the interview takes place. For example, the timing of a discussion about stopping active treatment depends on the patient's prognosis and condition. The difficulty with prognostication also impacts the ability to compare different health care units or institutions. It is possible that institutions will interview persons at different time periods prior to death. This situation may result in differences in observed quality measures that reflect timing of the interview more than differences in the quality of care provided.

Given these prognostication issues, an institution may do frequent interviews to capture the same time period from death across patients or relies on retrospective interviews with bereaved family members to collect information on a certain time period. Doing a prospective patient data collection has important advantages. First and foremost, the results could improve the quality of care of that individual patient. Second, the information originates from the patient and not a surrogate. Yet, retrospective interviews with bereaved family members remain an important tool to examine the quality of end-of-life care.

If information is desired about the last week of life, often a family member is the only person that is able to provide a consumer perspective on the quality of end-of-life care delivered to the deceased and his/her family. The advantage of this “mortality follow-back” approach is that the denominator can be precisely defined, given that demographic information (including next of kin) is reported on death certificates to state-level departments of vital registries. Thus, data collection can occur quickly without the costs of case finding for the prospective sample of patients. Because of this, mortality follow-back surveys have been used by both the United Kingdom (13,14) and the United States to collect (15) information on the last year of life of decedents.

WHAT ARE THE NEXT STEPS?

The first step in improving the quality of end-of-life care is taking stock—identifying and understanding the opportunities to improve. Simply stated, if you don't measure it, you won't improve it (2). Measuring or conducting an audit is the first step (Fig. 81-2). The second step is to engage stakeholders and define the goal. Engaging stakeholders means to present the results of the audit in a way that does not assign blame, but rather looks for the shared opportunities to improve and enhance the quality of care. Key to the success of this second step is raising awareness and developing a shared goal.

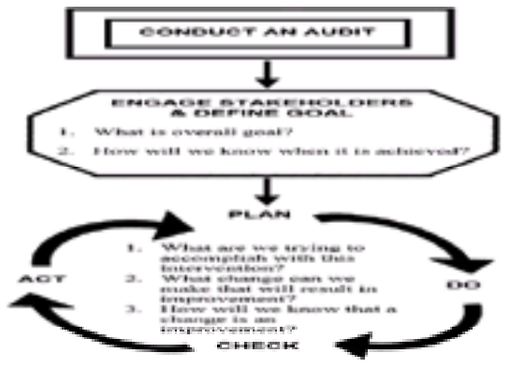


FIGURE 81-2. Quality improvement model.

The third step is actually improving the quality of end-of-life care through interventions and measuring whether these interventions succeed in creating change. Often, persons believe that education which provides knowledge and impacts attitudes will achieve change. Many times, though, knowledge is not sufficient to change behavior. Instead, changes must be made in the processes of care that provide the cues and default pathways that ensure persons will choose the right behavior. Often, this change can be achieved through a model of rapid improvement that utilizes multiple Plan, Do, Check, and Act cycles (PDCA) (16). PDCA cycles allow testing of interventions first on a small scale (sometimes as small as only one nurse with one patient). From the information learned, the intervention can be refined or a

different one can be tested.

Three key questions help to frame the work of the PDCA cycle. First, what is one trying to accomplish with this intervention? Just as an overall goal was identified in Step 2 of the quality improvement model, a goal must be stated for each PDCA cycle. Second, what change can one make that will result in improvement? This may involve brainstorming with a team of colleagues about what interventions can achieve the goal of the cycle. An effort should be made to be creative, yet don't be afraid to copy the success of others. Third, how will one know that change is an improvement? It is important to choose either a process or outcome variable that examines whether the goal of that cycle is being met and that data are tracked for the goal of that cycle, as well as the overall goal for the improvement effort. Often, a quality improvement team must test multiple interventions and conduct multiple PDCA cycles to achieve the overall goal.

CONCLUSIONS

Outcomes assessment is key to improving quality of end-of-life care. At this early stage of development of supportive and palliative care, we urgently need both research and quality improvement efforts that will contribute to the scientific evidence base. Care at the end of life is quite different than care at other time periods. Patients' informed preferences play an even more central role in decision making and outcomes. Not all persons with stage IV lung cancer, for example, will want experimental chemotherapy, and quality indicators must take into account that reasonable persons have different treatment preferences. Hence, measuring the quality of end-of-life care often requires interviews to examine the consumer perspective.

Even at this early stage, there are several promising measurement tools for quality improvement audits, for research, and for accountability. Selection of these measurement tools must be guided by the intended use of the data. The use of measurement tools for accountability carries two key requirements: an evidence base that suggests that the domain of interest is under the control of health care providers, and demonstration of satisfactory psychometric properties of the tool across settings of care.

With an increased focus on accountability, health care providers will need to become familiar with methods to improve the quality of medical care. Measurement plays an important role in quality improvement efforts—from the initial audit that raises awareness of an opportunity to improve, to ongoing assessments of whether interventions are achieving their goals. The ideal quality monitoring system for palliative care should strongly link guidelines and proposed quality indicators. Guidelines should be based on both normative and empirical research. Quality indicators can measure information about the structure of a health care institution (e.g., availability of certain services, existence of policies), about processes of care (i.e., the interactions of health care providers, patients, and family members), and about outcomes of care (i.e., the effectiveness of treatment).

Currently, most quality indicators measure either structure or processes of care. Outcome measures are intuitively more attractive, but they are more difficult to apply because of our limited ability to adjust for differences in patient characteristics and the relatively small numbers of people with a particular condition treated at institutions each year. One argument in favor of collecting process data is that they are a more sensitive measure of quality because adverse outcomes do not occur every time there is an error in the provision of medical care. Furthermore, important outcomes—both positive and negative—often appear months or even years after care has been given. Quality indicators based on measures of structure or process, however, are only as good as their ability to predict outcomes of importance.

ACKNOWLEDGMENTS

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RESEARCH ETHICS

DAVID J. CASARETT

The goal of good palliative care is to relieve suffering and to improve quality of life. However, it is apparent that access to palliative care is inconsistent, and standards to guide palliative care have not been established clearly. At least in part, these deficiencies exist because of a lack of solid evidence on which to base clinical decisions (1,2). Therefore, there is an urgent need for research that can provide evidence to define the standard of care and to increase access to quality care.

Recent years have seen a dramatic increase in palliative care research, defined broadly as activities that are designed to contribute to generalizable knowledge (3) about end-of-life care. This growth has created a heterogeneous field that encompasses both qualitative and quantitative techniques, and descriptive as well as interventional study designs (4). Although the past 10 years have seen impressive growth in all of these areas, this rate of growth appears to be particularly rapid for interventional research, including controlled trials of pain medications (5,6), interventional procedures for pain (7), and other nonpharmacological interventions to improve a variety of aspects of end-of-life care (8,9,10,11 and 12).

Despite the valuable knowledge that has been produced by this research and the promise of future important advances, its progress has been clouded by a persistent uncertainty about the ethics of these studies. Indeed, there have been concerns raised from several quarters about whether patients near the end of life should ever be asked to participate in any form of research (13,14). Others have objected to this extreme position (2,15). Nevertheless, many providers, Institutional Review Boards (IRBs), ethics committees, study sections, and even investigators remain uncertain about the ethical limits of research involving dying patients.

These concerns have considerable intuitive appeal and must be taken seriously. Indeed, it would be unfortunate if the progress of palliative care research were slowed by the sorts of ethical scandals that have threatened other fields of research that involve vulnerable populations such as those with mental illness (16). However, strict oversight and tight limits on palliative care research have the potential to do equal damage to a growing field. Therefore, to avoid potential scandals, without excessive regulation and oversight, it will be important that palliative care investigators and clinicians consider these concerns in a fair and balanced way.

This chapter discusses six ethical aspects of palliative care research that investigators and clinicians should consider in designing and conducting palliative care research. These include: (a) whether a study is research or quality improvement (QI); (b) the study's potential benefits to future patients; (c) the study's potential benefits to subjects; (d) the study's risks to subjects; (e) subjects' decision-making capacity; and (f) the voluntariness of subjects' choices to participate in research. Each of these is discussed, as well as opportunities to enhance the ethics of palliative care research in each of these ways.

DEFINING RESEARCH

The first, and arguably the most important, question that palliative care investigators face in designing an ethical study is whether it is research or QI. This decision is extremely important and has profound implications for the study's design and the ethical standards to which it will be held. For instance, federal law requires research projects to be reviewed by local IRBs to assure that informed consent is obtained from each subject, that research risks are reasonable in relation to expected benefits, and that subjects are recruited in an equitable fashion (3). In comparison, there are few widely accepted standards that govern QI.

In many situations, it is clear that a planned study is research. For instance, there is likely to be general agreement that randomized clinical trials comparing one or more pain medications or population-based studies of symptom prevalence, are research and should be held to the ethical standards for research. However, QI activities often share many of the attributes of research. For instance, both QI and research involve systematic data collection methods such as surveys and chart reviews. Both apply statistical methods to test hypotheses, establish relationships between variables, and evaluate outcomes. Both QI and research are designed to produce knowledge that could benefit patients other than those directly involved in the activity. In practical terms, therefore, QI and research activities are often difficult to distinguish. This can produce confusion and conflicting opinions from IRBs that review study protocols (17).

Unfortunately, the federal regulations that make the distinction between research and QI so important offer little practical assistance in distinguishing between the two types of activities. In those regulations, research is defined as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge” (3). Although elegant in its simplicity, this definition may prove prohibitively difficult for palliative care investigators to apply. It is often not clear how systematic an activity needs to be in order to be considered research. Nor is it clear how generalizability should be defined, or how an investigator's intent should be measured.

In an effort to make the distinction between QI and research more clear, additional criteria have been proposed. These include the degree to which a study deviates from standard care, whether an activity requires identifiable recruitment practices, how individuals are selected to receive a particular intervention, the degree of uncertainty associated with the intervention, and whether the patients involved benefit from the knowledge to be gained (18,19 and 20). One of the most recent of these criteria (20) describes a two-step algorithm that investigators may find useful when the existing criterion of an intent to produce generalizable knowledge (3) fails to provide adequate guidance. This algorithm is based on the additional risks or burdens that are imposed by a study and on whether the patients involved in the study will benefit from the knowledge to be gained (Fig. 82-1). Briefly, this algorithm suggests that studies should be considered as research, rather than as QI, if they expose patients to risks in order to generate knowledge that will not benefit them.

FIGURE 82-1. An algorithm that examines when quality improvement is also research.

This algorithm may prove to be too restrictive, as some have argued (21). In any event, it should not take precedence over existing federal regulations (3). It is, at most, a guide that palliative care investigators may wish to turn to. When the status of a project is unclear, investigators should also seek guidance from their own IRB.

BENEFITS TO FUTURE PATIENTS: A STUDY'S VALIDITY AND VALUE

Palliative care research is designed to produce knowledge that will advance understanding of end-of-life care. Implicit in this goal is the expectation that this knowledge will eventually improve care for future patients. Therefore, the first ethical aspect of palliative care research that deserves consideration is its potential benefits for future patients. These benefits to others can be described in terms of validity and value.

Validity

First, all studies must be valid. That is, they must use techniques of design and data analysis that peer reviewers can agree are appropriate. In addition, all studies must be designed to produce knowledge that is generalizable. Indeed, generalizability is the cornerstone of the Common Rule's definition of research: “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge” (3). These requirements collectively describe a study's validity (22). Validity is a threshold requirement for all research because it is unethical to expose human subjects to risks in studies that peer reviewers agree cannot adequately answer a research question (23). Therefore, at a minimum, investigators routinely consider a study's validity.

Value

Above this threshold of validity, palliative care studies may offer more or less importance or “value.” Broadly, value can be defined as the likelihood that a study's results will improve the health and well-being of future patients (24,25). Like validity, value is an important measure of a study design's scientific quality, but it is also a measure of its ethical quality. Value is an essential aspect of a study's ethical design because a central goal of research is to produce knowledge that will ultimately be “important” (3,26), “fruitful” (27), or “valuable” (28). In fact, one reason that subjects participate in clinical research is to produce knowledge that will benefit others (29,30). Because subjects are willing to accept risks and burdens of research, at least in part, in order to benefit others, investigators have accepted an ethical responsibility to maximize the probability that a study will be able to do so. Therefore, in addition to widely accepted scientific arguments for valuable research, there are compelling ethical arguments as well.

Maximizing Validity and Value in Palliative Care Research

Space does not permit a comprehensive overview of ways in which a palliative care study's validity and value can be assessed and improved. Indeed, such a discussion moves quickly beyond ethics and into the technical language of study design and health measurement. Nevertheless, several broad recommendations are possible.

First, a study's sample size should be adequate to answer the research question that is posed. Problems of underpowered studies, and particularly clinical trials, are both widespread and well described (31). But issues of power and sample size are particularly relevant to pain and symptom research, in which random variation can be quite large (32). To minimize these problems, it may be useful to establish consortia or collaborative groups that can participate in multicenter studies. Such arrangements have been highly effective in promoting research on rare disorders and may be applicable as well to palliative care research, in which investigators are limited and available patients are often sparse.

Second, palliative care investigators can enhance the ethical quality of a study by taking reasonable steps to increase the generalizability of its results. These steps might include sample size calculations that permit subgroup analysis of groups of patients that have typically not been the focus of investigation such as patients with noncancer diagnoses or elderly patients. The generalizability of a study's results might also be enhanced by recruiting subjects outside academic medical settings because preliminary evidence suggests that these patients, and their needs for care, may be different than those who receive care in academic settings (33).

In addition, palliative care investigators can enhance the generalizability, and therefore the value, of their research by making reasonable efforts to include patients who are receiving care at home and, particularly, those who are enrolled in a home hospice program. Substantial barriers may make it difficult to include these patients in research. Nevertheless, few data exist to guide the management of home care patients near the end of life, and palliative care investigators can enhance the value of their research by including this population whenever possible (34).

Of course, all of these improvements in generalizability come at a substantial cost. For instance, studies that recruit subjects from several different settings require more elaborate designs for recruitment and follow-up. In addition, investigators who include plans for subgroup analysis in their sample size calculations face rapidly escalating sample size requirements and costs. Nevertheless, steps like these offer an important way to enhance a palliative care study's value and, therefore, its ethical quality. Therefore, it will also be important that funding agencies understand the ethical importance of generalizability and that generalizability comes with a financial cost.

BENEFITS TO SUBJECTS

Palliative care investigators can also enhance the ethical rigor of a study by maximizing the benefits that it will offer to subjects. Broadly, these benefits can be considered under two categories: benefits to subjects during the study and benefits from the data that are collected. Each of these is discussed below.

Benefits to Subjects during the Study

Investigators may have several opportunities to maximize potential benefits of research to the subjects who participate. Perhaps the first, at least in an interventional study, is in their choice of an intervention. Ideally, a new intervention to be studied should have a reasonable chance of success. More important, though, if it is to offer subjects a significant potential benefit, an intervention should offer the possibility of a meaningful improvement over other interventions that are available to subjects outside the study. For instance, a pain management algorithm that is expected to reduce cancer pain (35) would only offer potential benefits if it is qualitatively or quantitatively different than those that constitute the usual standard of care. On the other hand, a comparison of two medications that are commercially available, such as topical fentanyl and sustained-release morphine, would not offer subjects any potential benefit. This is true even if the study's results offer considerable clinical value (36).

The potential benefits of a study can also be enhanced by choosing an active control design, rather than a placebo (36,37). If a placebo is used, a study's potential benefits can also be improved by altering the standard 1:1 randomization scheme in a placebo-controlled trial in a way that increases subjects' chances of receiving an active agent (6). The potential benefits of a placebo-controlled trial can also be enhanced by using a crossover design, so that all subjects are offered potential benefits, if the medication's pharmacokinetic profile makes it possible to avoid carryover effects.

These suggestions should be tempered by two caveats. First, the potential benefits of research are never certain. If they were, a randomized trial would not be ethically acceptable. That is, a legitimate argument for the uncertainty that justifies a clinical trial, or equipoise, could not be made (38). However, investigators generally design studies of interventions for which there is at least some evidence of effectiveness. Therefore, even though these potential benefits are not certain, they are more or less likely, and this assessment of likelihood should be considered in the design of pain research.

Second, palliative care studies need not always offer potential benefits. Indeed, many, and perhaps most, will not. Nevertheless, when a study does offer potential benefits, investigators may consider enhancing a study's potential benefits in these ways. The importance of doing so is particularly great if other aspects of a study raise ethical concerns, which might be the case if subjects' decision-making capacity is limited, or if the study's risks are substantial.

Benefits from Data Collected during a Study

Although the opportunities to enhance potential benefits described above apply largely to studies involving interventions, another opportunity applies equally well, if not better, to research that is descriptive. A common ethical issue in the design of palliative care research and, particularly, descriptive research, is the possibility that data

gathered may contribute to a subject's care. For instance, data gathered during a descriptive study may identify pain that is inadequately treated (39,40,41 and 42), dissatisfaction with pain management (43,44,45,46 and 47), or related clinical problems like depression (48,49).

In anticipation of instances like these, investigators can design standard operating procedures that help to ensure that valuable clinical information is made available to the subject and his or her clinicians. At the least, these procedures should include data about the presence of unrecognized and untreated symptoms, and concurrent disorders like depression. This is arguably an ethical obligation of symptom-oriented research (15). Moreover, these procedures offer a significant opportunity for investigators to enhance the potential benefits of pain research.

Benefits to Subjects after a Study Has Ended

Investigators can also enhance the potential benefits for subjects after a study has ended. These sorts of post-study benefits are not usually included in assessments of a study's balance of risks and benefits. They are also components of a study's value because these benefits generally come from the knowledge that the study produced. Nevertheless, subjects may benefit from the knowledge to be gained from a study if the study's results are applied to their care. Investigators have numerous opportunities to ensure that these results are translated into subjects' care and, by doing so, can enhance the study's potential benefits to subjects.

For instance, subjects in palliative care research can benefit after a study if they learn from the study's aggregate results. This might be the case if a study comparing two pain medications found that one resulted in fewer side effects overall (36). Subjects in the study would benefit from these data because this knowledge should allow them to make a more informed choice among available medications. Subjects might also benefit from results that are specific to them. For instance, if a subject receives two medications in a blinded, crossover trial, and prefers one to the other, he or she would be better able to choose between these medications in future clinical situations, armed with the results of a blinded comparison of the two (50,51 and 52).

Finally, investigators can increase the likelihood that subjects have continued access to medications that are studied. If medications are not available, either due to high cost or because the medication has not yet received regulatory approval, subjects will not benefit (immediately) from the study's results. Thus, by arranging reduced rate programs or open label extension phases, investigators can increase a study's potential benefits for subjects by helping to ensure that subjects will benefit from the study's results.

This benefit may be particularly important in palliative care research because mortality rates in some studies are very high. This means that subjects may not live long enough to see a study medication's approval for clinical use or to see a study's results published and translated into improved care. For this reason, it is especially important that investigators consider mechanisms by which results can be applied to the care of research subjects in a timely fashion.

MINIMIZING RISKS AND BURDENS

Investigators can also enhance a study's ethical soundness by taking steps to minimize a study's risks and burdens. Although the distinction between risks and burdens is not always clear, a rough heuristic is useful. In general, a risk can be considered as the probability of an adverse medical event or undesirable outcome. Risks might include side effects of a medication, or increased pain during a study. The term “burden” can be used to describe those unpleasant features of participation in a study that are more certain, and which are better thought of as inconveniences. Additional clinic visits, time spent filling out questionnaires, or time spent waiting in clinic might be described as burdens.

Identifying Risks and Burdens

Attention to the ethical design of pain research and to the minimization of research risks and burdens requires a clear agreement about how they should be defined. The criteria by which study risks and burdens are identified and evaluated use the concept of incremental or “demarcated” risks imposed by participation in a study (53). The application of this standard to interventional pain research would mean that investigators designing a trial to compare the effectiveness of two opioids (36) need not go to great lengths to justify the risks of the opioids being evaluated if subjects in the trial would have received similar medications, with similar risks, off protocol. Of course, the risks of any medication in a clinical trial should be disclosed in the informed consent process (3). Nevertheless, investigators are not under the obligation to minimize or justify these risks as they would be if, for instance, the same medications were being given to patients with mild pain who would not receive them as part of standard care.

Minimizing Risks: The Choice of Control

Perhaps one of the most contentious and emotional questions in palliative care research (54,55), and, indeed, in research generally (56,57 and 58), is whether a placebo or sham control arm is ethically appropriate. The ongoing debates about the scientific merit of these controls, and the competing advantages of active control superiority trials and equivalency trials, are beyond the scope of this discussion. However, several general points can be made about the ethics of placebo- and sham-controlled trials. Each of these designs is discussed below.

Broadly, placebos can be defined as interventions that are “ineffective or not specifically effective” for the symptom or disorder in question (59) Increased attention to the ethical issue of placebo controls in recent years has produced a growing consensus that all subjects in a clinical trial should have access to the best available standard of care (60). Thus, in infectious disease research, for instance, all subjects with meningitis would have access to an antimicrobial agent that has proven effective. However, this requirement may be difficult to apply to studies of treatment for pain, other symptoms, or depression, in which the placebo response can be quite substantial. These difficulties are compounded when the symptom being studied is transient such as incident pain (6).

For these reasons, it may not be practical to prohibit placebos in palliative care research, and a placebo control may be ethically acceptable in several situations. First, placebos are acceptable if subjects receive a placebo in addition to the standard of care. For example, subjects might be randomly assigned to receive an opioid for pain or an opioid plus an adjuvant agent. Second, a placebo arm is justified if the symptom under study has no effective treatment. For example, the transient nature of incident pain often defies adequate treatment on an as-needed basis, and a placebo control might be justified in a randomized controlled trial of a novel agent for the treatment of incident pain. Third, a placebo control is justified if subjects have adequate access to breakthrough, or “rescue,” treatment. This may, in turn, alter a trial's end points. For instance, the free use of breakthrough dosing in a trial suggests the possible inclusion of these doses as a study end point either directly (61,62) or as part of a composite end point (5,63).

Concrete recommendations about sham procedures are somewhat more elusive, in part because sham procedures themselves are difficult to define. In general, though, sham procedures in palliative care research involve the use of a control procedure, such as a nerve block, which is administered in a way that makes it ineffective (7). These procedures create ethical concerns because some subjects, or all subjects, depending on the study's design, are exposed to the risks of the procedure without hope of its benefits (56). Like placebo controls, though, shams also have a role in research, because the nonspecific, therapeutic effects of surgery may be substantial. For instance, Leonard Cobb's research in the 1950s effectively debunked a widely used cardiac procedure that, if it had been widely disseminated, would eventually have put thousands of patients at risk.

Investigators have an opportunity to reduce these concerns substantially in the design of a sham-controlled study. For instance, investigators might conduct these studies in a setting in which the procedure itself (whether sham or real) poses few, if any, additional, or “incremental,” risks above and beyond usual care. Investigators might insert a sham epidural catheter that would then be used for postoperative analgesia (64). When this is not possible, investigators can choose a crossover design, in which subjects are assigned to receive either the sham or the real procedure, followed by the other. This design does not decrease the incremental risks of the sham procedure. However, it does ensure that all subjects who bear the risks of the sham procedure also have access to the real procedure's potential benefits. This crossover sham design has been used in other settings (65) and might be appropriate for pain research when the risks or discomforts of the sham procedure are substantial.

Minimizing Burdens

For the most part, opportunities to minimize burdens are readily apparent. For instance, it seems reasonable, wherever possible, to minimize surveys, interviews, and additional study visits (66). These are all burdens that investigators routinely consider carefully in designing studies. However, there may be other needs and concerns that may be unique to, or more common in, patients near the end of life.

Although it is intuitively obvious that all research subjects would like to avoid the added time commitment and inconvenience of travel to and from additional appointments, this concern may be especially important to patients near the end of life, for whom long periods of time spent sitting in a car can exacerbate discomfort. Similarly, patients may view surveys and questionnaires not only as timeconsuming but also as a drain on their energy. Therefore, investigators who conduct palliative care research may have an added reason to minimize the burdens of extra visits and data collection procedures and to rely on telephone data collection strategies whenever possible.

Palliative care investigators may also need to consider the burdens that a study creates for friends and family members who often take on substantial burdens as caregivers (67,68 and 69). Although most of the burdens of research participation are borne by the subject, the requirements of time, travel, and, perhaps, time off from work, create burdens for others. Patients may be very sensitive to these burdens and, for some patients with chronic pain, burdens to others can be influential in the decision whether or not to enroll in a study (30). By building flexibility into a study design (e.g., use of brief telephone interviews, multiple options for timing of clinic visits), investigators may be able to reduce the burdens of research participation on others.

ENSURING DECISION-MAKING CAPACITY

Patients who consent to participate in research should have adequate decision-making capacity, which refers to subjects' ability to understand relevant information, to appreciate the significance of that information, and to reason through to a conclusion that makes sense for them (70). These concerns parallel concerns in research involving patients with dementia (71), psychiatric illness (72,73), and patients in the intensive care setting (74), among others. However, deficits in decision-making capacity may create several additional challenges for palliative care investigators.

First, concern about capacity is reasonable given the prevalence of cognitive impairment at the end of life (75,76,77 and 78). Cognitive impairment occurs in 10–40% of patients in the final months and in up to 85% of patients in the last days of life (76,77). Cognitive impairment may be difficult to identify in palliative care research because decisionmaking capacity varies over time (79) and because impairment may result from the experimental or therapeutic medications themselves, such as opioids, benzodiazepines, or corticosteroids (80,81). Investigators who conduct trials of medications will encounter these challenges even more frequently if trials are designed to evaluate treatments for delirium, for which impairment is an inclusion criterion (82,83).

Second, the effects of cognitive impairment on comprehension may be complicated by clinical depression, which occurs in between 5% and 25% of patients near the end of life (48,49,84,85 and 86). Clinically, significant adjustment disorders may be even more common (48). It is possible that these disorders may impair either comprehension or decisionmaking, or both (72), but studies have not yet supported this conclusion.

Third, even in the absence of overt cognitive impairment or depression, it is possible that severe symptoms or affective disorders may impair subjects' ability to understand the risks and benefits of research participation. For some studies, particularly clinical trials, the presence of one or more of these intractable symptoms is an inclusion criterion (87,88 and 89). It is possible that severe symptoms may impair comprehension if patients are unable to concentrate on the information offered in the informed consent process (90).

Finally, these challenges may be compounded in prospective studies that require participation over days or weeks. In these studies, even if patients have the capacity to consent at the time of enrollment, they may not retain that capacity throughout the study. Thus, days or weeks after patients give consent to participate, they may be unable to understand changes in their condition clearly enough to withdraw. The result can be a “Ulysses contract,” of sorts, in which research subjects find it easier to enroll than they do to withdraw (91).

None of these challenges is easily remedied. Indeed, it is obstacles like these that lead some authors to argue that patients near the end of life should not be allowed to enroll in research (13,14). Nevertheless, palliative care investigators have several concrete opportunities to enhance the ethical quality of palliative care research when decisionmaking capacity is uncertain.

First, at a minimum, investigators whose research involves patients near the end of life, who are likely to lack decision-making capacity, might institute brief assessments of understanding. Although this strategy cannot assess decision-making capacity, a few simple questions in either open-ended or multiple choice format provide a brief assessment of understanding (92,93 and 94). In some situations, investigators may wish to assess decision-making capacity more formally using validated instruments (95).

These sorts of safeguards need not be employed in all studies. Instead, their use should be guided by the prevalence of cognitive impairment in a study population and by the balance of risks and benefits that a study offers (34). For instance, when palliative care research involves only interviews or behavioral interventions that pose minimal risks, informal capacity assessments are generally sufficient. “Minimal risks” are defined as those risks that are encountered during a patient's usual care, or in everyday life (3). When research poses greater than minimal risks, but offers potential benefits, some assessment of understanding may be appropriate. This research includes studies that involve a placebo (6) or invasive interventions such as nerve blocks (96) or epidural catheters (97). When a study that poses greater than minimal risks does not offer potential benefits or is conducted in a population in which the prevalence of cognitive impairment is high (e.g., an inpatient hospice unit), a formal evaluation of capacity should be considered. This research includes studies that involve a placebo when an effective agent is available (5) and some pharmacokinetic/pharmacodynamic studies that require repeated blood samples and prolonged observation, without potential benefits (98).

If a patient does not have the capacity to give consent, a legally authorized representative may be able to give consent for research. This follows from federal guidelines governing research involving children (3) and is justified by the argument that surrogate decision makers should be allowed to consent to research just as they are allowed to consent to medical therapy. However, as with other research that involves patients without capacity to consent, investigators should be aware of applicable state laws that may restrict or even prohibit surrogate consent for research. In addition, investigators in this field should be alert to possible future changes in federal regulations that have been discussed (99).

If a patient does not have the capacity to consent but is still able to participate in decisions, investigators should obtain assent from the patient and informed consent from the patient's surrogate (100,101). This “dual consent” ensures that patients are as involved in the decision as possible yet provides the additional protection of a surrogate's consent.

If a patient has decision-making capacity intermittently, or is expected to lose capacity, investigators may obtain advance consent. This approach has been used in a study of treatment for delirium in which informed consent was obtained from patients while they had decision-making capacity (82). Advance consent should be obtained only for specific studies and should be obtained close to the planned start of research, for instance, at the time of hospitalization or enrollment in a hospice or palliative care program.

PROTECTING VOLUNTARINESS

Another way that investigators can enhance the ethical soundness of a study's design is to examine ways in which subjects' voluntary participation can be protected. In general terms, a choice is voluntary if it is made without significant controlling influences (102,103). At first glance, assurances of voluntariness appear to be an issue of informed consent, and, in fact, for the most part they are. However, a study's design and plan for subject selection and recruitment may have as great an influence on subjects' freedom to refuse research participation as does the informed consent process. In particular, two features of a study's design are relevant. First, a prospective subject's choice must be made with full knowledge of available alternatives (3). Second, his or her choice must be made with the understanding that he or she can withdraw at any time (3). Each of these creates opportunities in a study's design to ensure voluntariness, which are discussed below.

Reasonable Alternatives to Participation

First, investigators can make sure that a study recruits subjects from an environment with excellent standards of palliative care. If patients generally receive excellent care, they will be best able to make a free and uncoerced choice about research participation. If, however, patients do not have access to a bare minimum of treatment options and expertise, they may view research participation more favorably, out of desperation.

One solution, albeit a somewhat draconian one, would be to require that palliative care research be conducted only in settings in which patients have access to a full range of services, treatment, and expertise. Although this requirement would reduce the potential for research participation out of desperation, it would effectively limit research to a small number of academic centers, with a possible loss of generalizability (33). Another more practical option might be to include a lead-in phase when clinical pain research is conducted in settings where the standard of care is poor (15). A lead-in phase allows an opportunity to optimize palliative care prior to recruitment. This strategy not only has ethical value but scientific value as well because it provides a uniform baseline prior to randomization.

Opportunities to Withdraw

Investigators can also enhance the ethics of a study's design by ensuring that subjects are able to withdraw at any time. Although a subject's ability to withdraw should be a fundamental aspect of any ethical research (3), there may be unique barriers to withdrawal from palliative care research. For instance, subjects who withdraw from clinical pain research that involves one or more medications will usually need access to a different medication on withdrawal. This problem may be straightforward in many cases but can be very challenging in an interventional study if the investigational medication is an opioid, which requires the subject to get a new prescription and get it filled. Most states have created considerable barriers to opioid prescribing, including triplicate prescriptions, which may make it very difficult for a subject to obtain

a new prescription and get it filled in a timely manner. If a subject has his or her medication available, the process may be easier. Nevertheless, considerable challenges of calculating an equianalgesic dose remain. For both of these reasons, investigators can enhance the ethical design of pain research by developing mechanisms to ensure that subjects who drop out continue to receive adequate pain treatment with as little interruption as possible.

CONCLUSION

The field of palliative care, and the standard of care that it represents, depends upon rigorous research to provide data that will guide clinical care. Although this research raises substantial ethical questions, these questions need not curtail what promises to be a valuable and highly productive area of research. Of course, the concerns discussed above should be taken seriously. To do otherwise risks the sorts of ethical missteps that have produced scandals in other fields. Nevertheless, these ethical questions can be addressed through careful planning, attention to the adequacy of a study's design, and to the informed consent process.

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